LEUKEMIA & LYMPHOMA SOCIETY®

THE BLOODLINE WITH LLS

A PODCAST FOR PATIENTS AND CAREGIVERS

Episode: 'Transplant Support and Graft-Versus-Host-Disease (GVHD)'

Description:

Join us as we speak to Dr. Mariam Nawas and Dr. Satyajit Kosuri from University of Chicago Medicine, about graft-vs-host disease (GVHD) and the Transplant Optimization Program (TOP). In this episode, we discuss stem cell transplants, how GVHD occurs and what can be done to manage and treat symptoms. The doctors also share how the TOP program at the University of Chicago Medicine utilizes multiple specialties to improve post-transplant success for patients over 50.

Transcript:

Elissa: Welcome to *The Bloodline with LLS*. I'm Elissa.

Edith: I'm Edith.

Lizette: And I'm Lizette. Thank you so much for joining us on this episode.

Elissa: Today we will be speaking to Drs. Mariam Nawas and Satyajit Kosuri about graft-versus-host disease or GVHD after stem cell transplant. In addition, we'll hear about the University of Chicago Medicine Transplant Optimization Program and how it is beneficial to older patients who have received a transplant.

Dr. Nawas is a hematologist/oncologist at the University of Chicago Medicine who specializes in the treatment of leukemia and MDS as well as in allogeneic hematopoietic cell transplantation. Her research focuses on improving patient-reported outcomes and survival of older adults undergoing cellular therapy.

Dr. Kosuri is a medical oncologist and Clinical Director of the Hematopoietic Cellular Therapy Program at the University of Chicago Medicine. He treats adult patients with acute leukemia, myelodysplastic syndromes, myelofibrosis, and multiple myeloma. He

is experienced in stem cell transplantation with clinical research interests in improving patient access to transplant and preventing and treating graft-versus-host disease. He is passionate about guiding his patients through the treatment process and working with a multidisciplinary team of physicians to provide state-of-the-art care. Welcome Dr. Nawas and Dr. Kosuri.

Dr. Mariam Nawas: Thank you for having us.

Dr. Satyajit Kosuri: Hi, thank you. It's a pleasure to be here.

Elissa: So that our listeners understand the topic better, would one of you start by telling us what a stem cell transplant is.

Dr. Nawas: Sure. So, a stem cell transplant is a type of therapy that we give for people generally with blood cancers but also some other disorders. There are two main types when we talk about stem cell transplant. For short we call them auto (autologous) or allo (allogeneic), and the difference there is where the cells come from. In both cases, you start off with some kind of chemotherapy or radiotherapy; and then after that, either you get cells that we had previously collected from yourself and we reinfuse those in the patients or you get cells from a donor, and then we reinfuse those into the patient. And the purpose in the setting of leukemias and lymphomas is for that new immune system to battle the leukemia or the lymphoma that the patient has.

Dr. Kosuri: Miriam said something that was very important there is, knowing the purpose of the two types of transplants. So, for the auto transplants, what we're actually doing is we're administering the high-dose chemotherapy to help that patient overcome the resistance of their disease. We usually see this being utilized in multiple myeloma and lymphoma.

And we're not so much relying upon the stem cells themselves in order to control the disease. So it's really high doses of chemotherapy that are so powerful that they

cause a great degree of what we call bone marrow suppression. So if we were to give this to a patient and say, "Okay, we'll see you in clinic," they wouldn't recover their blood counts for many, many weeks. And so in order to prevent that from happening, we administer the stem cells taken from the patient prior to the chemotherapy. So they're literally rescuing themselves and repopulating themselves with their own stem cells, giving them a quicker recovery of what we call the hematopoietic or blood system and immune system.

Whereas on the donor or allogeneic transplant side of things, we're actually interested, and we actually want the immune system that comes from the donor and that eventually develops from that donor's stem cells to have what we call a graft-versus-disease effect, keeping away the leukemia, MDS, or myelofibrosis, whatever disease that they were originally transplanted for.

Elissa: So, is there a reason why somebody would have an allo versus an auto transplant?

Dr. Kosuri: Yeah, so what we know is that for certain disease types, and oftentimes we'll use this umbrella term called myeloid disease, and there's other diseases outside of that, but mainly when we look at the main utilization of allogeneic transplant, we're looking at diseases like acute myeloid leukemia. We're looking at myelodysplastic syndromes and myelofibrosis and then some of the chronic leukemias. There's another, bone marrow failure syndromes like aplastic anemia; and then ALL is another disease we use allotransplant for.

But basically, like I said, these are diseases we've seen over time where there is curative potential with an allogeneic transplant when we replace that bone marrow that isn't functioning correctly, and we allow a new immune system from the donor to take over and exert this long-term graft-versus-leukemia effect.

So those are the disease types that we know it works in and could be potentially cured with an allogeneic transplant. And then there are the other diseases, the lymphomas

and multiple myelomas where we see we can get potentially cure in some of the lymphomas with an auto transplant. And then multiple myeloma, we're looking for something called a disease-free interval, meaning we put people into remission; and we maintain that remission with high doses of chemotherapy.

And so it's something that we've seen historically, and that's how we divide patients up according to disease types when we're thinking about transplant. And, of course, nowadays with immune therapies and CAR T-cells, there is a little bit more nuance and variation when we choose the types of treatments and where we use them.

Elissa: Oh, that's very interesting. And so really then we're looking at a potential cure from almost a new immune system versus using their own immune system to help their counts get better faster and recover quicker and then stay in that remission.

Dr. Nawas: Yeah, exactly. So just to piggyback on that, for allotransplants, we use them when we think chemotherapy alone is not enough to put that disease in remission forever. And so the additional thing that you get with an allotransplant, besides the chemo, is a new immune system. It's immunologic therapy, and then auto we use for diseases that we think are responsive to very high doses of chemo. That's kind of an important distinction there.

Elissa: You mentioned it very briefly, Dr. Kosuri, but our topic today is graft-versus-host disease, commonly known as GVHD. So what is that and why does it happen to transplant patients?

Dr. Kosuri: Okay, so it's a good question. That has a very complicated answer. And I would say complicated sets of answers really. I often refer to GVHD as kind of the thorn in the side in the field of stem cell transplant. And I think for people to have a basic understanding of such a complex phenomenon, I often put it to patients within the framework of a story or a history lesson. And I also usually bring this up to medical residents and oncology fellows when I talk about GVHD and when I try to explain it, since it's very complicated.

So I'll try to be very brief, but just kind of going back in history, if we were to kind of step into a time machine, for example, and go back to the 1950s. This is post-World War II. We're in the Cold War era, and the field of stem cell transplant is starting to kind of become a concept, because we know with the threat of atomic bombs and radiation poisoning and what scientists had studied from the victims who had actually gone through nuclear explosions, we saw that, you know, if you put a living being through this type of stress or poison, what ends up happening is the body develops all sorts of complications.

And one of the complications that they noted is that there was a failure of the bone marrow. I tell patients, "Remember the bone marrow is an organ and it's where all our blood and immune cells, the white blood cells, red blood cells, the platelets are really born. So all of those cells that basically keep us alive are coming from the bone marrow." So the bone marrow's really important, and it's not something that people often think about as an organ like the heart or lungs or others when they think about the human body.

But anyway, what they found back in the day when this field was just starting to develop is that if someone were to develop or experience a bone marrow failure where they're not producing the cells, you could potentially take the parent cells or what we call stem cells to create a new blood and immune system like we're talking about. So take the stem cells from a healthy person and put them into someone who's bone marrow has failed, you could repopulate that bone marrow.

Early on, people were not trying this in human beings. They were doing it in mouse models and animal models, what we call them. And one of the stories that I often tell residents and fellows is about an experiment that I think is very important to understanding graft-versus-host disease; and it took place in the late '50s. There was a couple of scientists, Loutit and Barnes, one was French. One was British. They were working in the United States, and they were doing this very interesting mouse experiment where they were treating mouse leukemia with high levels of radiation.

Elissa: Oh, wow.

Dr. Kosuri: And they would essentially get rid of the leukemia, but the side effect, as we were alluding to here, is that the high level of radiation would cause bone marrow failure. So they said, "Okay, let's repopulate that bone marrow with stem cells and immune cells from a donor mouse." So they had two groups, and this is very pertinent to the development of GVH discussion.

Two groups of mice. One group of mice would receive bone marrow stem cells and immune cells from an absolute identical healthy twin mouse, okay? And then there was a second group that was receiving stem cells from a healthy random donor mouse. And what they found is after 100 days, the mice who received stem cells from their twin, genetically the same immune, immunologically the same, the blood system is the same, they were thriving. They were doing well. The leukemias were gone for the most part, their blood counts looked normal, and they were active. And then they looked at the other group who received stem cells from the random healthy donor mouse, and they were not thriving at all. They were actually dying off. They would find that they had skin ulcers, they were not eating. They were having diarrhea and just kind of wasting away.

And initially, they termed this secondary disease. They didn't really understand why this was occurring, and then with further research into the 1960s, they started to realize that this was being mediated by the immune cells from the donor mouse, specifically the T-cells against the body of the recipient mouse. So the transplant community was like, "Okay, we can't just take stem cells and the accompanying blood and immune cells from one living being and then throw them into another without trying to match them genetically." And that was the advantage of the twin mice versus the other group.

So the last thing that I think is pertinent kind of to understanding as a pillar of understanding GVHD is for patients and their family members is to understand that

everyone's immune system recognizes self and non-self. That's a very important concept because if the immune system identifies something as being non-self, it is programmed to do one thing. That is to protect by attacking.

So when you have transplanted immune cells in a new body, that's what we call the graft, okay, it can attack the host, which is the recipient who has received those cells. So that's where we get the concept of graft-versus-host disease from.

Elissa: Now how does GVHD manifest in people?

Dr. Kosuri: So GVHD, you can tell from the complexity, it can manifest in so many different ways. There is an acute form of graft-versus-host disease, and there's a chronic form. And this is an important distinction to make, that the transplant team will make because it will affect the way that they approach someone who has developed GVHD.

So, with the acute form, and this is oftentimes occurring right after someone has received an allogeneic transplant. You see people who may develop skin rashes, so the rashes can be kind of localized or they can be extensive. They may develop pretty severe and what we call refractory nausea; so, despite the use of various antinausea medications, they can continue to have nausea. They may throw up. They may have crampy abdominal pain as kind of the classic presenting symptom, and then diarrhea is another one. So the entire GI tract can be involved. And oftentimes when people are coming in for their clinic visits, we are checking their labs.

So another organ that's also affected for acute GVHD is the liver, so we may see what we call liver function test abnormalities that the patient may not really know about, but we'll be able to see on their lab tests.

And then if someone, for example, is kind of further out from their transplant, there is a presentation of chronic GVHD which can be all of the things that I just talked about; but people can also have, any other part of the body be involved. So they can develop

dry or very itchy, sensitive eyes. They can develop a tightening of the skin, and then lungs can be an issue. They can also be involved with chronic GVHD.

So it's a very wide variety of the way that it can present, so timing is important, whether it's right after the transplant or when someone's being tapered off their immune suppression. And then what organ systems are involved are also important. And these are the things that the transplant team is going to pay very close attention to because it's going to help them decide how to approach someone who's developing these signs and symptoms.

Dr. Nawas: I was going to say this is implied in what Dr. Kosuri said, but for GVHD, we really think about it with the allotransplants and not so much auto. It doesn't end up actually being that simple; but for the most part, we don't think of GVHD being an issue with auto transplants and that it's the allotransplants that we really have to look out for it.

Elissa: And then you mentioned the acute versus chronic. Does that then have to do also with how long those symptoms are going to last? Do some just only last a short time and then they relieve themselves or relieve with medication or do they just kind of last for the rest of your life? How does that work?

Dr. Kosuri: That's a really good question, and there's a lot of nuance that goes into that. I would say in general, when someone develops graft-versus-host disease, whether it's acute or chronic, the first thing that your transplant team is going to do is establish a diagnosis; and that may require a biopsy if it's feasible. But one of the things that I always tell patients who are going through this is that graft-versus-host disease is a clinical diagnosis. So biopsies can be helpful, but if a biopsy is not totally indicative of GVHD, it does not mean that it's not GVHD; and we will kind of approach it in that way, that it's graft-versus-host disease and we'll treat it and manage it accordingly.

Once we've established the diagnosis, we grade it and stage it. And what I would say is that even if it's something very mild, it's a skin rash that can go away with some topical steroids or it's pretty severe diarrhea that is having a difficult time responding to your regular antidiarrheal medications, both of those types, whether it's mild or severe, have the potential to respond really well to the initial mainstay of therapy which is steroids.

And what we will see is that people can either respond very quickly to steroids and respond very well to steroids and that we can taper steroids off in a matter of time, and that's different with both acute and chronic forms. Chronic, even when we have someone who's responsive to steroids, we oftentimes will take more time to get them off, to taper them off of that steroid and immune suppression versus acute.

And so it really depends on how the people respond when you're talking about duration of how long the symptoms are going to last. People who respond well, there is a higher likelihood that once the treatment is initiated and finally tapered off that they won't have to deal with it long term. But if people are not responsive or they become what we call steroid-refractory, steroid-dependent, then we're looking at more complicated types of graft-versus-host disease that may require more medications to be added on or a longer course of tapering.

Elissa: So there are a variety of medications to treat graft-versus-host disease then and the different symptoms somebody may have?

Dr. Kosuri: Correct, correct. Yes, and this can range, from topical ointments all the way to more intensive therapies; and that could be in addition to steroids, various types of immune suppression. Sometimes we even use various types of what we call ECP (extracorporeal photopheresis), which is a type of UV therapy where we actually treat the person's blood system.

So the type of treatments that are available fall under the umbrella of suppressing an overactive or what I would say rowdy immune system; and they run the entire gamut from something that's very mild to something that's more involved.

Lizette: Wow, it's good to hear that there are ways to treat it. And Dr. Nawas, you were saying that this is really seen more in allogeneic transplants than really autologous. We're really not talking about GVHD for autologous transplants. But does everybody that gets an allogeneic transplant get some form of GVHD?

Dr. Nawas: That's a great question. So it really depends really heavily on what we call sort of the type of transplant platform, which means exactly what the composition is of the graft. When we take the cells from the donor and we put them into the patient, are there T-cells, are we giving the patient a medication intentionally to try to reduce the number of T-cells? And all this falls under what we call GVHD prophylaxis, which is, an essential part of any transplant plan. We think about the chemo that we want to give the patient, we think about the donor, and then we also think about GVHD prophylaxis. Every transplant needs this.

Depending on what exactly is used for prophylaxis, whether it's medications before or after the transplant and immunosuppression, and also depending on how intense the chemo is that they get before the transplant. These things all tend to determine the rates of GVHD. So it is possible that someone goes through without GVHD. It's possible that someone gets acute and not chronic or vice versa.

As an extremely ballpark percentage, what would you say, Satyajit, like 40 to 60% of patients or something will have some amount of GVHD? But that's such a wide spectrum, so, having a mild skin rash, which actually, we find that to be a good thing for people to get a little bit of GVHD is not the same thing in terms of what it means to a patient's quality of life as having really more aggressive GVHD that's not so responsive to steroids and other measures. So, again, it really depends on the disease, the therapy for the disease, exactly the type of transplant, and the GVHD

plan. So once those factors are all personalized for the patient, they can have a more detailed discussion with their provider about what they think, kind of the rates of GVHD and so on will be.

Dr. Kosuri: I think that's an excellent point. I think that Dr. Nawas hit the nail on the head. I usually quote to my patients and their family members that taking all-comers, without getting too much into the weeds of how and what type of transplant, I mean there's so many different variables. But I would say about half of patients who undergo an allogeneic transplant will have some form of graft-versus-host disease. And that can range from the mild skin rash to the pretty severe diarrhea. But the important thing for patients and their family members to know is that the majority of these cases are going to be responsive to therapy. I think that's an important thing to establish.

And also, the other thing I say to some of my patients is that if you have a little bit of GVHD, as Mariam was mentioning, that is easily manageable, that is actually a good sign because that is telling us that the immune cells that you have received from the donor and the immune system that's developing withinside the patient is active. And it's actually probably doing the job that we want it to do, which is keeping that person free of whatever blood cancer that they received their allotransplant for. So that's important and you can kind of put it into like an analogy of you have a type of soup that you want to make, right? And every person makes that soup differently. So there's so many different ingredients to getting to the end product of a mushroom soup. And how much salt someone puts in there or the intensity of the conditioning or how many vegetables someone puts in there or why they're making that soup. It's so different for every person.

And so that is something that has to be taken into account when we're thinking about rates of graft-versus-host disease for each patient. But in general, I would say that Mariam's right, 40 to 60%. I tell patients about half the patients will experience it for all-comers.

Lizette: Yeah, that is interesting. I know Elissa does have somebody that she was told that, "Oh, some, a little bit of GVHD is good. Right, Elissa?"

Elissa: Yes, so I have a friend with AML, and she had stem cell transplant relapse, had a booster of the original donor cells. She did not get GVHD after the first transplant or again after the booster and then relapsed again, had a second transplant with a new donor; and then her doctors told her at that point, "We want you to get GVHD, at least a mild version of it because we want to know that the transplant is taking this time." So is that really just something that you're looking for, even just the mildest form, like just a rash?

Dr. Nawas: The tough thing about GVHD is that it's very hard to kind of divorce GVHD, so graft versus host from graft versus leukemia. So those things tend to go hand in hand, unfortunately. So, a graft that is very active against the leukemia may end up being the same graft that's also very active against the patient. And obviously we want one of those things and not the other; and so trying to kind of balance those two things is where the challenge comes in.

Dr. Kosuri: Yeah, there's a, definitively a fine line that your transplant team is going to have to walk because we, as Mariam's saying, we want to make sure that in patients who develop signs and symptoms of GVH that, either we're getting rid of the GVHD or we're making it extremely manageable to where we would like it not to affect someone's quality of life very negatively, but as we're trying to suppress this immune system, we are maybe potentially calming it down too much to where it doesn't do what it was supposed to do or what we intended it to do in the first place. So there's definitely a fine line and a very kind of delicate balance that transplant physicians and their teams will have to navigate when people develop symptoms of GVH.

Edith: Thank you, doctor.

Now, we know that many people of color have more difficulty in finding good donor matches for transplant. Does that affect the probability of developing GVHD?

Dr. Kosuri: Yes, so, you know, it's really interesting. Our center is in the South Side of Chicago. So as a percentage of our population who come to transplant, we see plenty of patients who are ethnic minorities in whom, in general, if they don't have a matched sibling, it becomes a little bit tricker to find a fully matched adult donor potentially in the registry.

And when we think about the risk of developing graft-versus-host disease, that goes hand in hand with matching. Right, so we saw that in the example of that mouse experiment. If we can get closer matches, the risk of GVHD theoretically goes down. And as we get further and further away from being a full match, the risk of graft-versus-host disease goes up because you are trying to put or mesh to a body and an immune system that have more genetic variability between them.

And so, it is an issue; and thankfully in the field of transplant there is a subset of transplant platforms that we call alternative donor transplants; and this is when we come across the issue of not being able to find a fully matched adult donor, whether this is a sibling or whether it's someone in the Worldwide Transplant Registry who's a full match to the recipient or the patient.

And over, I would say, the last 20 years, the field of alternative donor transplant has improved and has been refined and our ability to use different approaches for what we call graft-versus-host disease prophylaxis or prevention has definitely improved.

And so what we're able to do is even for our patients who are in our ethnic minority populations who don't have as many donor options potentially, we're still able to extend transplant to people who need them. So I think that's really, really important, and it's something that, in my training, previously I had given a significant amount of time to in regards to clinical research. So that is there. It's a good question. It's something that we have to deal with, but I think that we're improving transplant platforms to prevent graft-versus-host disease for alternative donors and extend access to patients who otherwise wouldn't have a very good donor option.

Elissa: That's really great to know. I know that organizations like Be The Match are really trying hard to increase the number of people of color to be donors so that there are more chances for good matches. But it is so good to hear that there are other alternatives for people if they can't find that perfect match in someone.

Dr. Kosuri: And the important thing as you're mentioning that is that there are clinical trials that are being designed specifically with this in mind. We want to extend transplant, we want to extend this platform to as many people as possible with these various blood cancers, but, also, we're paying attention to the fact that this is affecting a lot of people of color and we're still able to try to kind of build upon that and improve that and extend access to them in the process of improving kind of our overall approach to transplant.

Elissa: That's wonderful. Now once they do get close to their transplant, though I'm sure it's talked about prior to the transplant, I would think there's a bit of fear and anxiety that comes along with being told that you have developed some form of GVHD. So what do you say to patients at that point to help relieve some of their fears, their anxiety?

Dr. Kosuri: Based on what we've just spoken about, what I would say is that the first thing is don't panic, right. What I tell them are that there're many strategies to be able to treat graft-versus-host disease and many times to completely get rid of graft-versus-host disease, so they don't have to deal with it in the future. And if it's the type of graft-versus-host disease that sticks around, then we have many strategies that we can make it more of a manageable in the background type of scenario for many people.

And one of the things that I really drive home for my patients and their family members, because oftentimes the family members are real partners with the physicians and sometimes our patients may minimize or not remember to tell us everything, so family members, caregivers are extremely important. But the thing that

I always emphasize is even before someone is to develop graft-versus-host disease, please, please, please take your immune suppressive medications as instructed by your transplant team. Number one, you should take them. Don't skip a day. Don't think it's okay to miss them. If the transplant team calls you with an adjustment in the dosage, make that adjustment immediately; don't wait a few days.

And the reason I say this is that sometimes we see people are not totally compliant, and that's somewhat understandable because they're on 20 medications or more than that and they get very frustrated. But sometimes, when they're not compliant with their graft-versus-host disease medications, it can have very serious implications for their transplant success and also their long-term quality of life. So that's number one is to take your medications.

And let's say someone does take all their medications, right, and they still develop signs and symptoms that may be concerning for graft-versus-host disease, the main thing that they need to do is to report their symptoms as soon as they can to their transplant team. So it's not necessarily waiting for a few days and thinking that it's just going blow over even if it's something that your transplant team has a potential other reason for, "Oh it's the magnesium pills" or " you just ate dairy for the first time after your transplant. Whatever it is, let them know about it so they can kind of put into the back of their mind that this is going on because they're going to follow very closely what the duration of the symptoms are, what the severity of the symptoms are, how they're responding to other kind of supportive medications. So those things are very important.

So, yeah, I would say take your immune suppressive meds, don't panic if you develop signs and symptoms of graft-versus-host disease because there are many options to treat it, manage it, and make sure you tell your transplant team as soon as possible.

Dr. Nawas: Yeah, I think there's a natural tendency after transplant to want to downplay some symptoms. You know, patients have been sick for a long time, they

went through an intensive transplant, you want things to go back to normal, but it's really, really important – this is where the caregiver comes in – to give, like, a very transparent and honest history about symptoms. And so the earlier we can catch something like GVHD and intervene, the better it is.

Dr. Kosuri: Yeah. I can't tell you how many times you walk in, you look at the patient, "How are you doing?" "Oh, doing well." And then the wife or the husband will say, "Well, actually-"

Dr. Nawas: It's always the wife.

Dr. Kosuri: Yeah, the wife. Yeah. I'm trying to keep PC here, but it's always the wife. The wife will say, "Actually, yeah, he's not, he's been having some abdominal pain. The last three bowel movements looked like this or that." And then we're like, "Oh, okay, that's important because we're this many days out" or "Oh we've been tapering the tacrolimus." So, yeah, the caregivers are really our partners in all of this to get their family member and our patients through the whole process.

Lizette: Yeah, thank you. I think it's really important that you're mentioning the caregiver because the caregiver is such a big part of a patient's journey through transplant. And of course, we do advocate that patients do provide you with the most accurate information because what you're saying is that doctors can actually provide some type of treatment to alleviate some of the issues with GVHD.

Do you see anything coming in the future to relieve symptoms or reduce the chances of GVHD. Anything in clinical trials?

Dr. Kosuri: Yeah. I would say that there's actually a good deal of research going on in this field of graft-versus-host disease. Recently in the previous years, it's been both on the diagnostic front and a lot actually on the therapeutic front, so it's really important. So when I summarize to patients and their family members what's been going on in the field of graft-versus-host disease, there are a few points that I always

bring up. Number one, it starts from the beginning when we choose a donor. As the science gets better and better as we go, we will be able to continue to improve the degree of matching where we're able to, so that's important in reducing the risk of developing graft-versus-host disease.

More recently, over the past five years, ten years and even more recently right now, we've been using and extending existing prevention strategies or what we call graft-versus-host disease prophylactic strategies and using them in different transplant platforms with different donor types which is something where previously we were, I would say, more rigid in the way that we approached it. I think there's more flexibility nowadays than there was in the past because now we have more experience. And that's actually kind of building from the alternative donor platform that we were talking about previously.

And then, just think about it, we've been contemplating and thinking about graft-versus-host disease since the inception of stem cell transplant, so, you know, late '50s, early '60s in human beings, and we're still dealing with this here in 2021. So we've learned a lot about a very complicated issue and that we're able to see nowadays that there's other pathways, right, that we can potentially target with medications that we already have or using other immune therapies like antibody approaches both for prevention and for treatment even for the difficult-to-treat GVHD.

And so we're looking outside kind of the traditional areas that we investigate, so, more recently there's been the microbiome is a very important and growing field. There's been a lot of research in the transplant field of how the microbiome affects the risk of developing graft-versus-host disease or how does the microbiome affect a person's ability to respond to various therapies? How do they immune reconstitute or how does that immune system, that new immune system grow up in the person who's received the stem cell transplant?

So I would say that there's a positive trajectory, and that's even for the difficult-to-treat cases. I would say the scientific and the pharmaceutical communities are seeing this finally as an area of unmet need, and there's an effort to address this population by either including them in clinical trials or actually creating clinical trials that are centered around them. And, more recently, we've had two FDA approved medications which could be helpful for a difficult-to-treat population. So I would say that we are slowly getting to the point where we're adding more tools in the toolbox and already tools that we've had in the past we're learning how to use them in new ways.

Elissa: That's great. Now you both are clearly passionate about, not only making sure that patients do have a successful transplant but also that you are trying to relieve as many symptoms as you can posttransplant to kind of keep them moving forward through remission and, hopefully, a cure. So one of the things that University of Chicago Medicine has that you are both at, there's a program called the Transplant Optimization Program, or TOP for short. Could you tell us about this program and the benefit that it has for older patients?

Dr. Nawas: So, the transplant optimization program or the top program is something unique that we have at the University of Chicago and is unique among transplant centers and it was created in response to the fact that even though blood cancers are far more common in older patients. Older patients are actually far less likely to be offered a transplant by their physician compared to younger counterparts, you know, historically physicians worry that if someone was in there late 60s or late 70s that maybe they were too old or too frail to tolerate a transplant and they were really kind of making that judgment based on a patient's age and based on really simple measures. Something we call a performance status, which is essentially like an eyeball test. And we know that you know patients in this age range are really a diverse group of people. You can have someone in their late 70s who is exceptionally fit and then conversely you can have someone even as young as in their 50s but has gotten really beat up with chemotherapy and,and cancer treatment and has started to develop

some frailty, so you know this performance status in this age is is not enough to make a determination about whether or not you should offer someone a transplant. And so, the purpose of TOP is to do a more comprehensive evaluation of a patient's fitness. And so, the way that we currently have it setup - we see everyone over age 60 who is being considered for allo transplant and they will come into the TOP clinic and spend the morning with us and they will see a bunch of different providers. So, they'll see the transplant team, they'll also see an infectious disease doctor to talk about any you know infectious complications that they may have had so far in their cancer treatment. They will meet with a social worker. They will meet with a nutritionist, and they meet with a physical therapist. And we do all kinds of testing beyond just lab work. We will do testing of a patient's mental health of their cognitive health and then we'll do a lot of performance-based tests where we'll test a patient's strength by looking at their grip strength. We'll test how mobile someone is by looking at how quickly they can get up and walk across a room and believe it or not these tests actually tell us a lot about how well or not well someone might be able to tolerate transplant. And so the purpose is to determine who is and is not a good candidate for transplant and then to also find the people that might be somewhere in the middle that might just need some things intervened on and to come up with a plan for those people to think about how can we optimize whatever these issues are before transplant in order to make the transplant as safe as possible.

Elissa: Now then are they seeing these specialists after the transplant as well and continuing on with them? How long does that continue?

Dr. Nawas: So we do some visits after transplant and it really depends on the patient. So we have our nurse practitioner who's excellent who will see these patients after transplant, and definitely the day 30 and, and day 100, we have a more focused assessment looking at some of these things that we looked at pretransplant just to make sure that there's no deterioration in a patient's functional status, in their quality of life; and if there is, what can we do? But the sort of beauty of TOP is that it comes

very patient dependent and so if there is someone before transplant that we are particularly worried about nutrition maybe or weight loss, we know to watch that person more closely after transplant. So the pre-transplant evaluation kind of helps determine what to look for after.

Dr. Kosuri: Mariam, you touched upon it a little bit in your first where you were mentioning the introduction. We often talk to patients and their family members about, you know, they say, "Hey, they're 70-years-old. Can they undergo a transplant?" And we always mention physiologic age, what is physiologic age and what does it mean in regards to the outcome of a stem cell transplant? Can you kind of give a little bit more detail and build upon that in regards to what we talk to our patients about?

Dr. Nawas: Yeah, absolutely. So we like to say the biological age is really just a number. And saying that someone is 70, again, this is a very diverse group of people. There's people in their 70s who are exceptionally fit, and so physiologic age is really the age that that person functions at. So I like to ask patients, "How old do you feel? You might be 76, but how old do you really feel?"

Elissa: That's a good question.

Dr. Nawas: The other beautiful thing about TOP is that you get a lot of data from the patient. It's not just data looking at labs, looking at bone marrow biopsies. It's the person themselves telling you how they're doing and how they feel and what they think they can tolerate. And that becomes really hugely informative and, in some settings, even more informative than even the doctor's assessment of a patient's functional status. So hearing it from them and hearing what they think are physiologic age is really very helpful.

Elissa: Wow! That sounds like just a really good program. Now what results have you seen in patients in this program as compared to those who have had kind of standard pre- and post-transplant support?

Dr. Nawas: Absolutely. So there's a lot of research that comes out of this clinic. And one recent publication that we had was exactly this. It was looking at how did patients do before we implemented TOP at the University of Chicago and then comparing them to patients of the same age, the same disease, same disease status, how did those patients do after we implemented TOP? And really, there's a tremendous improvement. And primarily that comes from not just that the disease is better controlled. That's not necessarily. It's that the toxicities surrounding transplant that become an issue in older patients are much better tolerated in patients who have been seen in TOP and optimized in TOP. And so they're far less likely to run into kind of life-threatening infections or organ damage or other things once we've seen them in TOP.

Dr. Kosuri: I think that's really important because we oftentimes will get the question from a patient and their caregiver going into the transplant process, "What is the definition of success of a transplant?" I usually tell them, "There's two pillars to that answer. Number one is that we control your disease, and the disease is gone, it's cured. That's what we would like to see with the allotransplant.

And then, number two," as Mariam is alluding to, "there's something called, there's like an umbrella term transplant-related mortality or what is the percentage risk of dying from the complications of the transplant itself?" There's so many different things that come up after a transplant that can cause major complications. If we pick the top five, for example, you could say, "Infection, infection, infection, infection in graft-versus-host disease that relates to infection."

So, the TOP approach is very much geared towards how do we decrease the risk of transplant-related mortality that is inherent in this procedure by making or addressing any specific issues that the patient may have aside from their disease coming into the transplant so that they have what we call physical reserve, right? We need to have the physical reserve to be able to deal with the bumps in the road that will come after a transplant. You hear anecdotes of your colleagues telling you, "This person flew through transplant and did fine," but that's very rare. The infections are going to

come. The other bumps in the roads are going to come, so do they have the physical reserve to be able to get through them? I think that's the important thing. That's where Mariam and the TOP program really focuses on getting those patients in the best shape and condition possible or addressing their needs before having to deal with them after the transplant.

Dr. Nawas: The other definition of success that I would add, it's not just survival for patients, is that they survive, and they have a good quality of life. You're not really doing someone a favor if you put them through transplant, the leukemia's gone but they have terrible GVHD and they're not doing well, they're on medications. That's not what we consider a successful transplant. The whole purpose is to give someone their life back. So we want to see people thrive and do well eventually after transplant and so we really focus on quality of life and, again, hearing that from the patient.

Elissa: That's really good to know.

Edith: So, this question is for each of you. On our patient podcast home page, we have a quote that says, "After diagnosis comes hope." Based on your experience of working with transplant patients and those who have developed GVHD, what would you say to transplant patients to give them hope for the future?

Dr. Nawas: I think I speak for both Dr. Kosuri and myself when I say that we went into transplant among the different areas of oncology because it's a really unique and remarkable thing to be able to tell someone that you could offer them a cure. Not all Oncologists are lucky enough to be able to tell their patients that. Sometimes the best that you can do is some treatments that might prolong survival but won't actually take away the disease. And so, it's a really wonderful thing and I try to tell patients that when they're seen in transplant clinic, this is actually a time to be really hopeful and to be optimistic that maybe this is your opportunity to really put the disease behind you and, of course you're not in this alone, like Dr. Kosuri said, the caregiver is so important in the journey. We as a transplant team are absolutely here for you and all

of us will work together to make sure that this transplant is absolutely safe as it can be and that your quality of life is preserved as much as possible.

Dr. Kosuri: Yeah. Mariam really kind of summarized it is that the most important words – she just said it earlier – is that we want to give people their lives back, right. I love it when we see that, oh, this person's back at work and I haven't heard from them in a while because they're back to life. Or you get transplant physicians and nurses and physician assistants, nurse practitioners we all often will get pictures, right, of someone running a 5K or doing a marathon, or whatever it is.

So the goal of this for us is always been let's give you your life back. Let's put this disease and the transplant process itself, which is, in itself is a long-term process, let's get it to be in the rearview mirror. And how do we do that? Well, we do that with, number one, the experience of the transplant team. Whenever I tell patients who come to see me for a new consultation and they're, maybe from out of town, for example, and they're saying, "how do I choose where to go or what to do?" I always tell them, " We're viewing you as a family member." Number one, you need to go to a place that has the experience of doing transplant, the type of transplant that you need." And it's not just the experience of the physicians. It's the experience of the nurse coordinators. It's the experience of the advanced practice providers. It's the experience of the nurses up on the floor where they're doing the transplant, the social workers, the entire team, so that's really important. And I think in the field of transplant, we're finding that there are so many team members that we can add on to improve the outcomes and the quality of life of patients going through this process.

And then the other thing as we gain experience in this field is when we're thinking about GVHD, is that clinical trials where we were using new approaches, to make transplant a more manageable, less toxic, and overall successful procedure for someone long term so we can get to that point where we say, "Okay, we're able to help them get their life back."

And as Mariam has just been talking and focusing on here in the last few minutes is, if you looked at transplant, just look at the change as far as hope is concerned. If you looked at transplant 25 years ago, if you were over the age of 50, "Sorry, transplant's not for you." Right.

That has changed. Then it went to, "Oh, you're 60. Sorry, we can't do transplant." And now we're oftentimes looking at people in their mid to late 70s and getting transplant consults, and it's not some sort of crazy idea. And especially with these programs like the Transplant Optimization Program [TOP], where we can get people through and get them through with good quality of life.

So I think all of that is very hopeful. We are in a state in the field of transplant now that's just going to continue to improve and where you can just see historically the change that just happened over the last couple of decades has been immense. So that's something that's important.

Elissa: That's really great. I love that you said, "Our goal is to give the patients their life back." I love that. Thank you so much for joining us today, Dr. Nawas and Dr. Kosuri. I think this will be so helpful for transplant patients or patients, maybe who've just gotten diagnosed and they're looking at transplant and just hearing about GVHD and what they could go do and all that hope for the future that their symptoms could be relieved, or we could prevent the GVHD in the future. That's just so great. So, thank you so very much for joining us today. We really appreciate it.

Dr. Nawas: Thank you so much for having us.

Dr. Kosuri: Thank you. We really enjoyed it, and I hope that, , any of the information that we've, talked about today can really help people either after the transplant or even before the transplant so they can understand what they may have to go through or they can understand that, there are other options for them if they need it and that, people who are in this field we care very much and, we're constantly trying to improve.

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