LEUKEMIA & LYMPHOMA SOCIETY®

THE BLOODLINE WITH LLS

A PODCAST FOR PATIENTS AND CAREGIVERS

Episode: 'Beyond the Transplant: Navigating Graft-vs-Host Disease (GVHD)'

Description:

A stem cell transplant for blood cancer is just the beginning – what may come next for the patient can be a complex journey. In this episode, Dr. Alison Loren of the University of Pennsylvania discusses graft-vs-host disease (GVHD), a possible complication of transplantation - exploring the latest advancements in treatment and how patients and caregivers can navigate the challenges ahead.

Transcript:

Elissa: Welcome to *The Bloodline with LLS*. I'm Elissa. Thank you so much for joining us on this episode.

Today, we will be speaking with Dr. Alison Loren, Chief of the Division of Hematology/Oncology and Professor of Medicine at the Perelman School of Medicine at the University of Pennsylvania. She is also the Director of the Blood and Marrow Transplant and Cell Therapy and Transplant program at the Abramson Cancer Center. Dr. Loren specializes in hematologic malignancies and hematopoietic cell transplantation. Her clinical and research interests focus on outcomes in transplantation, fertility preservation and pregnancy, and long-term survivorship. Welcome, Dr. Loren.

Alison Loren, MD: Thank you so much, Elissa. I'm so glad to be here.

Elissa: So, our episode today is on graft-versus-host disease, or GVHD, which is a common complication of stem cell transplantation.

Dr. Loren: That's right.

Elissa: But before we get further into GVHD, let's start with the basics. Could you explain stem cell transplantation and why it is an effective treatment for many blood cancers?

Dr. Loren: Sure, absolutely. So, hematopoietic cell transplantation, which people sometimes refer to as hematopoietic stem cell transplantation, or stem cell transplantation, or blood stem cell transplantation, or bone marrow transplantation- it goes by a lot of different names, but it's really all the same idea, which is basically to treat a person who has a serious blood cancer with, usually a conditioning regimen, which is considered preparation for the infusion of the stem cells.

So, basically, the patient will first receive chemotherapy and sometimes radiation therapy; and then there is an infusion of someone else's blood stem cells. And those blood stem cells are expected to travel to the bone marrow space and set up shop and start making new healthy blood. Many patients are in the hospital for that whole treatment, although there are some programs and some regimens where the patients can be treated as an outpatient with very frequent follow-up in the doctor's office.

It typically takes two to three weeks for those new donor cells to start growing in. That's a process that we call engraftment. And eventually we expect that the new donor cells will completely take over and that the person will be left with an entirely new blood system.

The advantages of a stem cell transplant or a bone marrow transplant are that it can eradicate any leftover cancer cells that might still be in the body after the prior treatments that a patient might have received to treat the original cancer.

But one of the really important aspects of a donor bone marrow transplant is that, in addition to replacing the cancerous blood with healthy blood, it's a really important thing to know that the immune system is part of the blood system. So, when we replace the blood system, we're also replacing the immune system.

The immune system has a very important function in keeping us healthy. The way the immune system works is it knows what is your own self and what is something that's foreign to you or different. In a regular person, when a germ enters your body, the immune system will notice the germ; and it'll say, "Oh, that looks foreign, and I better attack it." It doesn't know that it's a germ. It doesn't say, "Ooh, that's the flu virus. I better kill you." What it says is, "You don't look like me. I better kill you."

And so, when we replace the immune system in a bone marrow transplant, there are two really important effects that come from that. One, is that the donor immune cells can recognize cancer cells as foreign and try to kill them, and that's a really powerful immune effect from transplant that we call the graft-versus-leukemia, or graft-versus-tumor, or graft-versus-lymphoma, whatever the cancer is graft-versus-tumor effect. And basically, what that is, is the donor immune system fighting off the patient's cancer, and that is one of the main reasons that people can be cured with a bone marrow transplant.

Unfortunately, even in 2025, our immune systems are still not very well understood. Sometimes, the donor immune cells will attack the healthy body tissues in a patient, and that's the syndrome known as graft-versus-host disease. The graft, the bone marrow source, the bone marrow graft is attacking the host, the person who's now having the bone marrow in them. And so, graft-versus-host disease is, essentially, an immune reaction where the donor immune cells are attacking healthy body tissues in the recipient.

Elissa: I'm sure people listening right now are thinking when you said that the donor cells will come in, a new immune system will come in and see the cancer cell as an invader, they might be thinking, "Hey, I was healthy before I got cancer. Why didn't my immune system see that cancer cell as a problem and attack it?"

Dr. Loren: That is such an awesome question, and it really is one of the many million-dollar questions in immunology. We really don't understand very well why it is

that a person's own immune system wouldn't recognize cancer. There's a lot of theories about it, including things like the cancer sometimes can evade the immune system by secreting certain chemicals or factors that might mask it; or it looks so much like the patient's own healthy stem cells that it can't tell the difference. For whatever reason, the immune system has some sort of blind spot against the cancer. So, we don't really understand that, but that's a very active area of research, trying to understand why cancers happen in the first place.

Because if you think about it, cancers happen when there's a mistake in the replication or the growth of all of our normal healthy cells; and actually these errors are happening all the time, and most of the time our immune systems are able to detect those abnormalities and get rid of them before they turn into cancers that we experience. And so, clearly, it's the case that some cancers are able to get through the fence; but we don't really understand why that is.

Elissa: Okay. Now, when you were talking about stem cell transplant earlier, you talked about the use of donor cells, so an allogeneic transplant versus using somebody's own cells, which is an autologous transplant. Could you share the differences with these?

Dr. Loren: Sure, absolutely. I'll start with which diseases do we treat with each type of transplant. So, autologous stem cell transplants, as you just said, are using the patient's own blood stem cells. And so typically, what will happen is a patient will undergo stem cell mobilization where we give certain medications to stimulate the bone marrow stem cells.

Usually stem cells only live in the marrow. They don't live anyplace else in the body. They don't live in the bloodstream. But with certain medications, we can stimulate those stem cells to leave the marrow and circulate in the blood. And then the patient will undergo a procedure known as apheresis, which is an outpatient procedure where the blood stem cells are able to be collected from the blood itself through usually an IV

catheter of some kind. The cells are then frozen, and then the patient gets their conditioning regimen, and then those cells are taken out of the freezer and defrosted and infused back into the patient.

That procedure is typically used for patients with blood cancers known as lymphoma and multiple myeloma. We sometimes also use that treatment for people with other kinds of tumors like testicular cancer. That's fairly rare. And it is starting to become used for even certain noncancerous diseases like certain rheumatologic or autoimmune diseases.

An allogeneic transplant, as you pointed out, is when we use stem cells from somebody else; and we usually do that in situations where the patient's own bone marrow is so sick or damaged that we can't use it. And so, for instance, for people out there who have acute myeloid leukemia (AML) or acute lymphoblastic leukemia (ALL), we know that those bone marrows are irreparably damaged in the vast majority of patients. If you have one of those conditions and your doctor feels that you need a transplant, it's because we don't think that your bone marrow will ever be healthy enough to give you a long healthy life. And so, for those people, it wouldn't make any sense, even if you're in remission, to take out your own cells and then give them back to you because, for the most part, we think they're not healthy.

Elissa: Right.

Dr. Loren: There are some very rare exceptions, so I want to make sure that your listeners understand that very occasionally there are situations where people with acute myeloid leukemia or AML will be recommended to receive an autologous transplant. It is not commonly done in the United States; but it is something that sometimes can be very helpful and curative treatment. So, I just don't want to be too general in the way that we're talking. And probably the biggest difference between those types of transplants from the patient's experience is that with a donor transplant,

because we're giving you somebody else's blood stem cells, there's a chance of rejection, meaning we could give you those cells, and you could kick them out.

And then, of course, there's a risk of graft-versus-host disease, which we talked a little bit about already, which is based on the fact that those cells are coming from a different person. Your body looks foreign to them; they look foreign to you; and so, because of that, there's usually a need for treatment to prevent rejection and to prevent graft-versus-host disease. Whereas, with autologous transplants, because it's your own self, you don't need those kinds of treatments.

Elissa: So, speaking of that, we recently had a patient write in to ask about a rare syndrome called autologous GVHD. Now we haven't often heard that a patient could have GVHD after an autologous transplant using their own stem cells. And just from how you described how GVHD comes about usually with the foreign immune system coming in and not recognizing your own body, what is that syndrome, and how is that possible?

Dr. Loren: Right, I know, it seems like it shouldn't be possible, and I don't know that anybody has a great answer to that question either. I think the way that we think about it in the transplant world is that when we do these transplants, they typically involve, as I mentioned, pretty intensive chemotherapy and sometimes radiation therapy. And we hypothesize in that setting that perhaps there's been some kind of reset of the immune system or that the collection of the cells had somehow activated the immune cells in the graft; and so, there's some way in which the patient's own cells have somehow become sensitized to the rest of their body.

And if you really think about it, it's not that shocking, right, because if you think about the whole field of rheumatology, which is what we call autoimmune diseases, diseases where the patient's antibodies or immune cells are attacking their own cells, right. That's what lupus is, that's what scleroderma is, that's what idiopathic thrombotic purpura or ITP is. That's what autoimmune hemolytic anemia is. There's a lot of

examples or situations where the immune system becomes dysregulated and attacks itself, attacks its own native tissues, even though it shouldn't.

I think, autologous graft versus host is sort of like a writ large version of that, that somehow those donor cells have become recalibrated, reactivated. And so, when they get put back into the patient's body, even though it should be an exact match, something has ticked off those donor cells now and they're just attacking.

Elissa: All right, yeah. That makes a lot of sense, actually.

So, we know that GVHD is a pretty common complication, but does it happen to everyone who receives stem cell transplant?

Dr. Loren: No, it does not.

Not everybody gets graft-versus-host disease, even with a donor transplant. We typically expect somewhere between a third and a half of all people to get some form of graft-versus-host disease. Those numbers, it's really a moving target because one of the really exciting things that's been happening in the transplant world is we're learning new strategies to reduce the risk of graft-versus-host disease. And we can talk a little bit more about that in a bit. I'm sure that's going to be something of interest.

Elissa: Absolutely.

Dr. Loren: And so, it may be as few as a quarter of patients in some situations; and a likelihood of getting graft versus host depends on how closely matched the donor is and other certain donor features as well as, to some extent, the preparative regimen and also the graft-versus-host prophylactic regimen that's chosen.

And I'll say to all of our listeners that transplant is all about tradeoffs. If there was one easy way to give everybody the safest transplant that's going to cure everyone and

never cause graft-versus-host disease and have no long-term problems, we would do that.

So, part of the arch of bone marrow transplantation is understanding your patient, understanding the disease that they have, understanding the donors that are available, and then selecting a prep regimen, a donor, a graft-versus-host regimen that's going to, in the transplanter's best estimation, maximize all the good things and reduce all the bad things. But there's no such thing as a perfect transplant.

Elissa: Okay, so if it doesn't happen, does that mean the transplant wasn't effective?

Dr. Loren: It does not mean that, and that's one of the great, I would say, confounding things in transplantation. I tell this to my patients all the time. You can be cured or not cured from your transplant; so, it's important to know, unfortunately, that not everybody who gets a transplant is cured. It's possible for the cancer to come back after transplant. Obviously, that's something that we really hate to see, but it happens sometimes.

And you can get graft-versus-host disease or not. And so, there are some people who are cured and never get graft-versus-host disease. That happens maybe a quarter to a third of the time. There are people who have, unfortunately, both. They have graft-versus-host disease and their cancer relapses, and then there are all the other potential combinations.

We are really still in the very early stages of understanding how we can leverage the donor immune system for good. We need to cure the cancer but not have any of the bad side effects of graft versus host. And what I tell my patients is that that is the Holy Grail of bone marrow transplantation. If you can figure out how to cure people with no graft-versus-host disease, you'll win the Nobel Prize.

Elissa: Absolutely. Yeah, that sounds like a pretty good deal if we could do that for everybody.

Dr. Loren: Yes, exactly.

Elissa: So, what are the different ways that GVHD may affect someone? Can it affect multiple parts of the body at the same time?

Dr. Loren: Yes. So, graft-versus-host disease, I always tell my patients it comes in two flavors, acute and chronic graft-versus-host disease. And a long time ago, we used to characterize those by timing. We would say, "If you got graft-versus-host disease within the first 100 days after your transplant, that's acute; and if it happens later than that, it's chronic." But really in the more modern era, we've come to think of it as two very different syndromes because the timing can be really significantly affected by lots of other factors, including the graft-versus-host treatment plan and the type of transplant that you get.

So, acute graft-versus-host disease is typically manifested by either a skin rash, gastrointestinal symptoms, or liver abnormalities. It can affect any organ, but those three are usually the ones that are affected. It can affect one or two or all three of those organs. And acute graft-versus-host disease can be very mild. For a rash, it could be just like a sunburn-like rash that doesn't even really bother somebody, or it might be a little itchy.

But it can progress and be very serious. We have rarely had patients who have like head-to-toe blistering red rash, sometimes where the skin is peeling. We've had, in fact, some very severe situations where people have to be in an intensive care unit for all of the skin care that they need. It's almost like a burn victim.

And similarly, with the gastrointestinal version, a mild form might be some nausea, or some weight loss, or a little bit of vomiting, or diarrhea. But the very severe versions can involve significant amounts of diarrhea. Again, sometimes even requiring hospitalization because there's so much volume loss from the diarrhea.

And with the liver, sometimes we just see abnormalities in the blood tests that measure liver health. But sometimes patients can develop really severe liver symptoms where they are yellow, and they have fluid in their bellies and other liver-related complications.

I will say that I know that all sounds really terrible, but the vast majority of patients have the milder forms; and it's single-digit percentages of people that have those really severe forms of graft versus host.

I'm trying to talk in this program the way I talk when I consent my patients I feel that to go into a bone marrow transplant with your eyes open and understand that graft versus host can be a really serious complication, but I also don't want our listeners to feel scared off by a bone marrow transplant because usually it's being offered because that is your best chance to be cured from a really tough cancer. We never undertake these decisions lightly, and so even though we know that the graft-versus-host risks, they're never zero and there is a rare chance that they could be really serious, we are advising to get a transplant because we think the benefits outweigh those risks.

Elissa: Yeah. I had AML, and I remember my doctor told me when I first got diagnosed, we were talking about stem cell transplant as a possibility for the future, but he was like, "Listen, I don't want you to get this unless you need it."

Dr. Loren: Yeah, exactly.

Elissa: "It comes with complications, and so if we can get you cured with chemo, then that is what we're going to do." And that is what happened. I responded very well, but I was glad that he really prepared me but also said that we don't want to put you through that unless-

Dr. Loren: Absolutely.

Elissa: -we absolutely need to. And because it can cure AML.

Dr. Loren: Yes.

Elissa: And, so, we want to do that if we think that that will be the thing for you.

Dr. Loren: Absolutely. And so, I didn't know that about you, so, congratulations on your great health, and you look wonderful.

Elissa: Thank you.

Dr. Loren: And I will say that I share that approach. I call myself a reluctant transplanter. There's this old saying that "If you go to the barber, you're going to get a haircut." And, I really try hard not to practice that way, and to really think through with my patients whether a transplant is truly the right thing for them based on their overall health, the likelihood of their disease being cured without a transplant, how likely will they be to do well with a transplant, might they live longer without a transplant than with one? There are some situations where we now have really powerful therapies that can keep people in remission for a long time. And if they're doing well with those treatments and we only have really risky transplant options for them, they might not be better served with a transplant.

Elissa: Right.

Dr. Loren: And I think it's a really nuanced conversation for many people. There are some people who we know, because of certain features of their blood cancer, that they will not be cured without a transplant.

Elissa: Right.

Dr. Loren: And so, I think we sort of have to be really clear about that and to say, "Look, I have patients who are young and healthy with a really high-risk cancer; and even though they might be nervous about a transplant, we know what's going to happen without a transplant." And so, this is the best option that we have. We're still

really trying to make sure we give the best options to everybody, regardless of where they're coming from and where they start.

Elissa: Yeah, absolutely.

Dr. Loren: I realized I didn't answer the second part of your question about chronic graft-versus-host disease.

Elissa: Yes.

Dr. Loren: Let me give you a little bit about that.

Elissa: Yes, let's hear about that.

Dr. Loren: All right, so chronic graft-versus-host disease is a different sort of beast altogether from acute. It tends to come on slowly, and it affects many organs. Really, it can affect any organ. And it usually does affect more than one organ at a time.

Elissa: Okay.

Dr. Loren: Chronic graft-versus-host disease is, the medical word is protean, because it has many different forms. I guess there was some Greek mythology figure who could take on many forms, and so that's what we refer to it as.

And most commonly, patients will develop dry eyes, dry mouth, mouth ulcers, skin changes, which typically include things like thickening or redness or tightness. Sometimes, it can affect the joints and it can be hard for people to move well. They might notice that it's hard for them to raise their arms all the way up over their head, or to fully extend their arms, or to type fluently on a computer.

It can affect the hips and the knees and sometimes the ankles can get super tight, and so people can't walk as well as they used to. It's almost like a Frankenstein kind of walking because they can't flex their ankles.

It can affect the esophagus and the swallowing tube. It can get narrow. It can affect the lungs, so people can have trouble breathing. It can affect the liver. I think those are the most common places that we see signs of graft versus host, but it can affect the muscles. People can have pain or inflammation. It makes people tired. Graft-versus-host disease is a highly inflammatory condition. It really takes peoples' energy away.

People who have acute are more likely to get chronic, but there is not a perfect correlation and rarely people can have nothing, and then slowly develop graft-versus-host disease chronic later on.

Typically, if you're going to get a form of graft-versus-host disease, it happens in the first one to two years. It's unusual to have no graft versus host at all and then all of a sudden in year three it comes in. So, that's another thing to remember. I know a lot of people may not live close to their transplant center, and they're getting follow-up with their local hematologist/oncologist. I would just say that if you're like four or five years out from your transplant and you never had graft-versus-host disease and now something weird is happening, it's pretty unlikely for it to be graft versus host. Somebody thoughtful should be investigating what's going on and not just chock it up to graft-versus-host disease if you've never had it before and you're a long time out from transplant.

Chronic graft-versus-host disease, both of these are actually diagnosed, usually with the right clinical scenario. But sometimes biopsies can be helpful. There are certain tissue changes that give us a lot of information and also sometimes can exclude other reasons why you might have a certain symptom. Like, for instance, with a skin rash, sometimes it's an infection or a virus, and so getting a biopsy can help us sort that out.

With the liver, there's a million things that can go wrong with the liver, so getting a biopsy to prove that it's graft-versus-host disease and not an infection or some other

form of a drug-related inflammation or something like that. So, it's another really important thing.

The treatment of graft-versus-host disease usually entails steroids like prednisone in pretty significant doses, as well as other medications that have side effects. We want to be sure that we're treating the right thing before we embark on a treatment plan. I would say most of the time it's pretty clear what's going on, but every so often you need to be thinking about other things too.

Elissa: Okay, so besides prednisone, what other ways can this be managed, and can it be prevented?

Dr. Loren: Yeah. Those are, actually, two great questions and there are separate answers. So, for treatment, this is another place where there's been, actually, a lot of exciting progress. When I first started, it was just prednisone and then you were on to like sometimes using older drugs like cyclosporine, or putting people back on tacrolimus, which is an immune suppressive medication we often use with transplant, or even sometimes using chemo because that was the only way that we had of shutting off the immune system.

And now, we have had a lot of really exciting progress in the last sort of five to eight years with several new drugs being approved to treat graft-versus-host disease in both its acute and its chronic forms. And so, drugs like ruxolitinib, ibrutinib, belumosudil are all FDA approved for treating graft-versus-host disease. And there are new drugs coming down the pike all the time. A drug that was just approved called axatilimab seems to be very effective, particularly for chronic graft-versus-host disease, especially for people who have the really tight skin and joints, which can be a huge quality-of-life issue. That medication's particularly effective there.

We're understanding that graft versus host in the lungs can be treated with sort of a triple combination of an inhaled steroid, an antibiotic, and an asthma medication. So, there's definitely some progress in treating graft-versus-host disease; and we're really

seeing some great responses to treatment. And sometimes, people can actually eventually be tapered off all of their medications, and they don't end up needing to be on anything for the long haul, which is really an important quality-of-life issue.

Elissa: So, it can be resolved?

Dr. Loren: Yes, it can be resolved. And then there's some really cool clinical trials that are open that seem to be very promising. I really encourage people who are experiencing graft-versus-host disease, if you're being cared for in an academic medical center or really any center that has clinical trials available for graft-versus-host disease, I really encourage you to think about participating in the trials. Not only might there be benefit to you from getting a drug that seems promising but also, most importantly, you're really helping future patients. None of this progress would be possible if we didn't have people in the past who had graft-versus- host who are willing to participate in clinical trials so that we could learn and understand which drugs work, which drugs, importantly, don't work and that we shouldn't be using. So, if you have access to research, I really strongly encourage you to think about participating.

In terms of prevention, we're also learning a lot there. And I would say that the single most important advance in preventing graft-versus-host disease maybe ever, since the beginning of transplant, is the use of actually an old drug called cyclophosphamide or Cytoxan®, which is a form of chemotherapy. And giving, I would say, sort of small to moderate doses of that medication after the transplant.

So, the usual course is to give Cytoxan on the third and fourth day after the bone marrow graft or stem cell graft has been infused. And it seems that when you do it that way, I'll just oversimplify and say the bad T cells, the bad immune cells that are going to cause graft-versus-host disease, those seem to replicate really early. And so, if you give the Cytoxan on days 3 and 4, you seem to wipe out those bad guys and create an environment where the more accepting T cells, the ones that will fight leukemia but not cause problems, seem to be able to proliferate and survive. And the

introduction of that process, which was really pioneered probably about ten years ago in the setting of people receiving transplants from donors who are not matched to them, and we haven't talked about matching yet, but maybe want to talk about that for a minute.

Elissa: Yeah.

Dr. Loren: But it seems like it works really well, even in people who have matched donors.

And so, there was a big research paper, I don't know, maybe two years ago now, that showed a significant improvement in people living long time after transplant without graft-versus-host disease and without their cancer coming back, and they have a better quality-of-life. That data was just published last week, and so, it really seems like this strategy, which people refer to as PTCy or post-transplant Cytoxan, is a really important way to prevent graft-versus-host disease.

So, that's been super exciting. And, there are new drugs being pioneered and tested every day. One of the tricky things is that sometimes we have like three different trials and they all show positive results. But they're comparing different things to different things. So now you have three different treatments that all work better than the old way, but you don't know whether against each other how they're going to do. So, now we're starting to try to compare the better one in this trial against the better one in that trial to see which is the really better one.

And then, of course, what's also exciting is that we're also developing new stuff all the time too. So, in a way, it's hard for the research to keep up with the research, if that makes sense. There's all these new drugs coming; and then we have these large randomized trials showing something helps. So, it's a really exciting time from a research perspective. We're finally starting to see some real improvements in people living longer after transplant with less toxicity, less graft-versus-host disease. It's a really important, time in bone marrow transplantation.

Elissa: Okay. Now you brought up matching and so, finding just the right donor for the patient. It sounds like that's pretty important when it comes to potentially preventing GVHD, correct? Could you talk a little more about that?

Dr. Loren: Yes. I'll start by saying that, you know, medicine is still way smarter than doctors. And so, sometimes even with a match, even with a donor that we think is the lowest possible risk of graft-versus-host disease, we still sometimes see really severe cases of graft-versus-host disease. We still get surprised, unfortunately, so I just want to say that there's no guarantees.

When we talk about matching, we are looking at a set of proteins that are referred to as HLA. It stands for human leukocyte antigens. HLA encodes their genes that encode for a set of proteins; and those proteins are on every single cell in your body, and that is the way that the immune system knows what is self and what is foreign. So, taking it back to the very beginning of our conversation, we said that the immune system protects us by recognizing self-versus foreign. The way it does that is by, your immune system knows which HLA proteins are yours, and if there's something on the surface of another cell that doesn't look like you, that's how it knows what to attack.

You'll hear people refer to a donor as an 8 out of 8 match or a 10 out of 10 match. Basically, what that means is, remember, that you get half of your genes from one parent and half of your genes from the other parent. HLA is encoded all together on one of your chromosomes, one of your packages of genetic information. You'll have 5 proteins from your mom and 5 proteins from your dad, and that adds up to 10. So, if a donor is matched in all 10 of those places, we call them a 10 out of 10 donor.

Those places have names. They're not very interesting names. They're HLA-A, HLA-B, HLA-C, HLA-DR, and HLA-DQ. It turns out that DQ doesn't matter very much. You can be not matched to DQ, and your outcomes are just as good. So, then we have 4 on each chromosome, and that makes 8. So, that's what we mean when we talk about an 8 out of 8. That's a perfectly matched donor, an 8 out of 8 donor.

So, if you remember your high school biology, a brother or a sister has a 1 out of 4 chance of inheriting the same packages of genetic information that you did.

Elissa: Yes.

Dr. Loren: And so, we always like to type brothers and sisters first because there's a 1 in 4 chance that they could match you. And that doesn't sound like a very high number except, I'm going to tell you that there are millions of HLA proteins out in the world. So, any other random person has like a 1 in a million chance of matching you.

So, when you think about it that way, a brother or sister being 1 out of 4, that's pretty good. Not to be confusing, but a brother or sister also has a 50/50 chance of being a half-match with you. A half-match means they inherited one set of proteins from one parent that's the same, but from the other parent, they inherited the other set of proteins that that parent has.

A half-match donor is also called a haplo. You'll hear people refer to haplo donors. And we know now that haplo donors are actually great donors as well.

Elissa: Oh, good to know.

Dr. Loren: It also turns out that, and if you think about it for a second, it's sort of obvious. A parent or a child is guaranteed to be a half-match because you've either inherited half their genes, or you've passed half your genes along to your kid. So, all parents and children are haplo or half-matched.

In addition, there is a registry which was formerly known as the National Marrow Donor Program, but now they just go by NMDP because there's so many different kinds of transplants. They didn't want to restrict themselves to marrow.

So, the NMDP is the donor organization that helps to facilitate bone marrow transplants from volunteer unrelated donors. So, there are many, many millions of

people who have volunteered to donate blood, stem cells, or bone marrow if they're found to be a match with somebody.

So, I know I just told you that anyone random person, it's like a 1 in a million chance that they're going to match a patient. But the registry has many, many millions of people in it so, the likelihood of finding a match is decent. It turns out, it's actually not evenly distributed. Because these proteins are inherited together, these genes are inherited together, they tend to sort by genetic ancestry.

One of the very upsetting and challenging facts about the registry is that people who identify as White have about an 80% chance of finding a matched donor in the registry whereas, people who identify as Black have only about a 30% chance of finding a match. That's, obviously, hugely discrepant and makes it impossible for us to deliver the very best care to everybody, which is, of course, always our goal. And so, the NMDP has engaged in a lot of campaigns to try to bring more diverse donors into the registries so that we can always find a match for everybody.

But one of the really most important contributions of this PTCy strategy, this post-transplant cyclophosphamide is that it seems to be so good at preventing graft-versus-host disease that you don't even have to be a perfect match, and you could still have a really good outcome from your transplant.

What that advancement has helped us to do is to safely do transplants, even if the donor is not a perfect match. So, those half-matched or haplo transplants from a family member, or even a 7 out of 8, or a 6 out of 8, or a 5 out of 8 from the registry, those are all seeming to be very safe transplants. We do have data that a 7 out of 8 donor in the registry is just as good as a perfect match. Less well-matched donors we're still learning about.

The last thing I'll say, is that another really important source of donor stem cells is umbilical cords. Some people talk about this like umbilical cord or cord blood transplants. The way that we obtain those is when a person is delivering a baby,

depending on where they live, there might be a public cord blood bank; and they are offered the chance in the delivery room, to access the placenta and to collect umbilical cord blood stem cells. Those are cells actually from the baby, but they are removed from the placenta, and they're stored in a bank.

And those cells are kind of magical. They're very enriched in stem cells and they're very good at replicating. So, you don't need very many of them to have a successful transplant. And because they're naïve, they're brand new coming from a newborn baby, it seems that they're much more flexible. You don't need to have a perfect match to do a successful cord blood transplant. So, cords have also become a really important source for people who don't have matches.

So, again, lots of graft options; and your transplant expert will help determine what they think is the best graft source for you. And I will just say as a public service announcement for your friendly bone marrow transplant doctors, please don't go to your doctor and tell them you want this kind of transplant or that kind of transplant. It is not like ordering from a menu at a restaurant. I have had people say to me, "I would like a cord blood transplant please." And I'm like, "Okay, that might be the right thing for you, or it might not." So, your doctor should be able to go through all the graft options with you and explain why they think that one or the other might be the best one.

Elissa: Right. That is very good advice. You've gone over a lot of the medications now for both treatment and prevention. Are there any emerging therapies or those on the horizon that you're particularly excited about?

Dr. Loren: Yes. I'm reluctant to be very specific because I think there's a lot of trials underway and a lot of really promising options. And a lot of similar trials. Like, several different drugs that are all targeting the same pathway or the same target.

What I'm most excited about, honestly, is not any one particular drug or cocktail. What I'm really excited about is our ability to scientifically understand the pathways

and the contributors to graft-versus-host disease, because what I envision someday is that instead of this kind of, "Well, let's try this because it works for most people," "Oh, it didn't work for you. Okay, let's try this other thing." And you sort of get to a point where, oh, each drug has a 30 or 40% chance of working, and so, we're just going to try this one and that one and the other one. And one of the really big challenges, especially with chronic graft-versus-host disease is that sometimes it can take two or three months before you even know if something's working. So, it gets pretty exhausting, and there's a lot of side effects that happen along the way.

Where I think we're heading is the ability to sort of profile a person's graft-versus-host disease, where we're going to be able to say, "Okay, these inflammatory markers are elevated in this person" or "This person has a profile like that," and "This person has a profile like this." And we know that drug A works best for that kind of profile, and drug B works best for that kind of profile. I think we're going to be able to get a lot smarter about understanding and treating graft-versus-host disease.

And I'll give you an example from my own practice. I have a patient who had really, really severe acute graft-versus-host disease after her transplant. She enrolled in a clinical trial. That drug worked for her. She did great, but then she later developed chronic graft-versus-host disease, which wasn't that surprising because she had really bad acute graft-versus-host. And so, we treated the chronic our usual way,prednisone, ruxolitinib. She did great. She wanted to come off her medicines. We stopped her medicine, and her graft- versus-host flared up again.

I had noticed something in her blood work that made me think that a treatment that was a little bit different from the usual graft-versus-host treatments would work for her. And so, I gave her that treatment instead when her graft-versus- host recurred. And knock wood, she's been doing great. So, I do think that's like a really, like, second grader example of where we are right now. But I do think that we're going to be able to better characterize graft-versus-host and then pick treatments that are personalized, based on how people's graft-versus-host shows up.

Elissa: Okay, so essentially, targeted medicine for GVHD, just like-

Dr. Loren: Yeah.

Elissa: -we're shooting for targeted medicine for the cancer.

Dr. Loren: Yes, that is a much more succinct way of saying what I just said, yes.

Elissa: Okay. So, with all of this, I would imagine that finishing treatment and then continuing to have GVHD affect your life can have an emotional impact for the patient. How can patients emotionally manage GVHD into long-term survivorship?

Dr. Loren: That is such an important question, and I think a lot of people think like, "Okay, well, I'll just get my transplant and it'll be like really bad for a year, and then I'll be done." And for some people, that actually is what happens. But for most people, that's not what happens.

And, I think it can feel like a real setback or a real blow, especially when people develop graft-versus-host disease sort of later down the line, like they're eight or nine months out from their transplant and then they get graft-versus-host. And they're like, "I thought I was done. I thought I made it." And then they have this sort of bump in the road.

What I really encourage people to think about - number one, graft-versus-host disease can be really hard to live with; and it really can, unfortunately, limit you. It can increase your risk of infections. It means you're taking chronic medications. It might mean that you can't get certain vaccinations because there are live vaccines, and so you can't get them. You're going to be more concerned about going to crowded events, because you're worried about getting sick. So, it really is a huge impact on your quality-of-life.

And, some people have almost a paradoxical where they're like, "I know I'm lucky, I'm cured. I'm three years out from my transplant, and I should just be grateful. I

shouldn't feel this loss, or I shouldn't feel sad about this because I know so many people don't make it this long." So, I would just say, yes, you're lucky, but it is okay to feel sad and to mourn the loss of those things that you can't do or won't do or shouldn't do. So, don't feel bad about feeling bad. It's just like having any other chronic illness.

Elissa: Yeah.

Dr. Loren: And that's not fun for anybody. So, it's okay to feel sad, even though you're also grateful. Those are two complicated things to sort of hold in your head.

And, the other thing I do try to remind patients is that, in general, and this might be changing, but from everything we know about graft-versus-host, it does seem to protect people from their cancer coming back. And so, I do try to encourage people to remember a little bit of silver lining, to maybe say a little prayer of gratitude for those donor T cells that are a little too busy in there-

Elissa: Yeah.

Dr. Loren: -that they're doing good work and keeping the cancer away. And it is really hard to adjust. I mean that phrase "new normal" is so overused, but it's exactly what it is.

And I think seeing a therapist- Actually, I have a couple of patients who have managed to find therapists who specialize in people with chronic illness.

And I think that can be really powerful because I think, sometimes, even therapists will say, "You should be grateful. You're cured of your cancer." And that's really hard for people to hear.

Elissa: Yeah, it's not particularly helpful. And they want to feel validated that it's okay to feel these things. It's okay to feel whatever you're going to feel.

Dr. Loren: Right. That's a great way to say it.

Elissa: Yeah.

Dr. Loren: And I think it really is a loss. It's mourning your normal life that you have to adjust and live differently. And people are angry about that. People are sad about that. They experience a lot of life changes. They aren't happy with their appearance. They can't go back to their exact same job. The research in this area shows that many, many, if not most patients who undergo transplant, they may not be able to go back to their previous, everything's the same. They can't go back to their normal job. They can't do as much as they used to do.

I will say, although some elements of that are normal, there are also certain things that happen to people after transplant like thyroid disease, or lung disease, or heart disease. So, I will say that if you're feeling really poorly, it is appropriate to look into that. There is a level of acceptance. But if you're really not feeling well, you need to talk to your team about that because sometimes there is something wrong, and that can be addressed.

Elissa: Absolutely, yeah. Definitely communication with your treatment team is very, very important.

Dr. Loren: Yes.

Elissa: And to our listeners, we are absolutely holding space for you today to feel however you're going to feel after your cancer diagnosis if you have GVHD symptoms. So, thank you for saying all that.

So, our final question today, on our patient podcast home page, we have a quote that says, "After diagnosis comes hope." What would you say to patients and caregivers to give them hope after a stem cell transplant?

Dr. Loren: That is a great quote, and I totally agree with that. I feel like we are in the business of providing hope. I would say, number one, we're able to offer transplants to more and more people, partly because of the advancements we already

talked about, partly because we're understanding that transplants are safer even in older people where we previously would have thought that they were not young enough to get a transplant. We're definitely expanding the availability of transplants to people, offering a chance of cure when there wasn't one before.

I think the treatments of blood cancers are getting much more sophisticated and safer, which means that more people are able to get to transplant because they haven't suffered a complication of their treatment before the transplant.

I think our ability to diagnose and recognize and treat risks of transplant are ever-increasing, and we're able to do transplants more safely than ever before.

So, I guess what I would say is that people think of leukemia as the worst possible thing that could happen. And it is really serious, obviously. But you're a great living example of this. There's so many treatments that we have to offer. I mean, yes, it is a devastating thing to hear and to have to go through. But what I tell my patients is that, it's going to be a really tough year, but then we're going to put this in the rearview mirror; and we're going to move forward. And part of my job as a transplant physician is to help you understand what to expect, how to manage to be ready for problems or complications, and to be prepared to handle them, and to teach resilience so that our patients can sort of roll with whatever comes. And I feel so lucky to be practicing in this field at this time because there's just so many better ways of doing things.

Elissa: Yes, it is an exciting time in blood cancer with so many new things coming out, new treatments for GVHD, new treatments for blood cancers, and so, yes, definitely an exciting time.

Well, thank you so much, Dr. Loren, for joining us today and telling us all about stem cell transplant and GVHD. I hope that our listeners learned something today and can go back to their doctor and talk more about their options and what's available to them. And so, thank you so very much for being here with us.

Dr. Loren: Oh, thank you for having me. It was really fun talking to you. This was great.

Elissa: And thank you to everyone listening today. *The Bloodline with LLS* is one part of the mission of The Leukemia & Lymphoma Society to improve the quality of lives of patients and their families.

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We hope this podcast helped you today. Stay tuned for more information on the resources that LLS has for you or your loved ones who have been affected by cancer.

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graft-versus-host disease at LLS.org/GVHD. These links and more will be found in the show notes or at TheBloodline.org.

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