LEUKEMIA & LYMPHOMA SOCIETY®

THE BLOODLINE WITH LLS

A PODCAST FOR PATIENTS AND CAREGIVERS

Episode: 'Let's Talk About Stem Cell Transplantation: Benefits and Side Effects'

Description:

Please join us as we speak to Dr. Shernan Holtan and guest co-host from LLS, Christina Neilsen. In this episode, Dr. Holtan discusses stem cell transplants; how they work, the different types of transplants, and the side effects, including graft-vs-host disease (GVHD).

Dr. Holtan shares exciting new research on reducing GVHD and provides blood cancer patients with hope as transplantations continue to improve and bring about potential cures.

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 to Dr. Shernan Holtan, and our guest cohost from LLS, Christina Nielsen. Dr. Holtan is a hematologist/oncologist in the Blood and Marrow Transplantation and Cellular Therapy program at the University of Minnesota in Minneapolis. At that institution, she also serves as an Associate Professor of Medicine in the Department of Hematology, Oncology, and Transplantation. Her work is focused on improving the outcomes of hematopoietic cell transplantation by reducing graft-versus-host disease, or GVHD, and boosting mental and physical resilience.

Joining us to cohost today's episode is our colleague and LLS Patient & Community Outreach Manager, Christina Nielsen. As a key part of LLS's local outreach, Christina covers the Upper Plains Region of Minnesota, North Dakota, South Dakota, and Wisconsin. She helps connect patients and healthcare professionals, like Dr. Holtan, with information about LLS programs and services. Christina also organizes and

provides local services to the blood cancer community, such as live and virtual educational programs.

Welcome Dr. Holtan and Christina.

Shernan Holtan, MD: Thank you so much for this invitation. I'm very happy to be here with you.

Elissa: So, let's start with learning a little bit about you, Dr. Holtan. How did you start in medicine and what drew you to hematology/oncology and stem cell transplant research?

Dr. Holtan: Wow! I've always been interested in the human body. Going far back to childhood going to the library, I'd always check out anatomy and physiology books even when I was a kid.

When I went into medical school, I actually thought that I would end up in neurology. I thought the brain was really fascinating.

Elissa: Wow!

Dr. Holtan: And I still do. But, as I went through my rotations, I had some experiences that eventually led me to BMT. When I was a third-year medical student, I was very interested in dermatology, and I rotated with a physician who saw a patient in his mid-20s and had a head-to-toe skin rash. He had a bald head and it was clear that he had had some recent chemotherapy and radiation and was being treated for cancer. And I asked my dermatology attending physician what was happening, and she said, "This young man has graft-versus-host disease." This is a condition where his donor's stem cells have led to an inflammatory complication leading to a skin rash, and they did this for a treatment for leukemia." And I was like, "What? He has what? He has stem cells from another person in his body! How can this even be?" And she explained to me the concept of the graft-versus-leukemia effect, how someone can use

the immune system to, hopefully, cure cancer. And I just thought that was the craziest, wildest thing I had ever heard of and was just instantly drawn to the field.

Elissa: That's really fascinating. You said "BMT," can you tell our listeners what that is?

Dr. Holtan: Absolutely. BMT stands for blood or marrow transplant. Historically, our field used to say BMT was a bone marrow transplant. Nowadays, we refer to this mostly as blood or marrow transplant. This has some historical relevance. When our field was beginning in the 1960s, the source of hematopoietic stem cells was the bone marrow itself, and so donors would have a bone marrow harvest where somewhere between 1 to 2 liters of bone marrow might be extracted from the hips for transplantation. And that was the way that we got stem cells for all of our patients.

Well in the '90s and later, there have been techniques to mobilize the stem cells that live in the bone marrow and help them to circulate in the blood so that we can collect them using a machine called an apheresis instrument. So basically nowadays, a lot of the stem cell transplants are done collecting stem cells through this apheresis procedure, which is really like a fancy blood donation. A lot of times our donors don't have to go through a bone marrow harvest; they can donate stem cells using their peripheral blood.

Christina Nielsen: Thank you, Dr. Holtan. Our podcast today is on stem cell transplant. Can you talk more about that process and what that is exactly?

Dr. Holtan: Yeah, absolutely. So, stem cell transplant is a way to treat cancers, but it also can be used to treat metabolic or genetic conditions of the bone marrow as well. So historically, the way that we think about transplant is divided by, two main types, either autologous or allogeneic transplants. Autologous means you're using your own stem cells. So auto refers to self, and so there are a number of conditions where we can use our own stem cells for a transplant. This would include the more mature malignancies, such as lymphomas or multiple myeloma. And when I say mature, I

mean the types of cancer that arises in these lymphocytes or plasma cells they're more mature cells, so we call them more mature lymphoid malignancies. So, we can use our own stem cells in that case because the stem cells are still healthy. It's just these cancers that we want to treat using this modality.

Contrast that with an allogeneic transplant, that's where we're using stem cells from a different donor, a healthy donor, to treat a stem cell-related problem. So, for example, myelodysplastic syndromes or acute myeloid leukemia, acute lymphoblastic leukemia, these are less mature cancers or cancers of stem cells. That's why we can't really use autologous transplant to treat them. We do have to replace the bone marrow with somebody else's. We call this an allogeneic transplant because we're using stem cells from an allo source or a healthy donor.

I highly recommend going to your website, LLS, and learning more about these malignancies, as well as BeTheMatch.org. That also is a good website to go for additional information because, gosh, students, residents, fellows spend years learning this stuff. I think it would be really hard for someone who's just, learning about their own malignancy or their loved one's malignancy to try to wrap their heads around it. It is pretty complicated.

Rarely we can do something called a syngeneic transplant. That's where someone who has an identical twin can have that identical twin be their donor, and so we refer to that as syngeneic. But most of the time we're referring to either an autologous or an allogeneic stem cell transplant.

Elissa: Wow! I don't think I've ever heard of syngeneic before.

Dr. Holtan: I've seen a few. It's always fun when someone has a twin.

Christina: Dr. Holtan, can you talk a little bit more about the donation process and how you can find an appropriate match? What makes a person a good match?

Dr. Holtan: Yeah, absolutely. We match people based upon a system called the human leukocyte antigen or HLA. This is different from blood type. So, blood type refers to ABO, for example. With HLA, there are multiple different markers that we're looking at that helps define someone as who they are immunologically. So, we use these HLA markers to find our matches.

What we first do is we'll do a blood test to determine a patient's own set of HLA markers, and then we'll use that to compare against a potential donor. And usually, the donor will have that test done just by a cheek swab, so we can collect enough DNA just from swabbing the inside of the cheek to be able to test HLA in donors. A patient's HLA type will be compared against the HLA type typically from a cheek swab from a donor and they'll look for a degree of different matches. Really the minimum number that we're looking at is eight matches, so HLA-A, -B, -C, DR beta1, and DP and DQ if we go out to 10 or 12 markers, for example. We're looking at all of these different markers and seeing if we can find a match either within the family; and if we cannot find one within the family, then we're looking at the BeTheMatch.org or the National Marrow Donor Program.

Each sibling has about a 25% chance of being a perfect match with the recipient. When we look at the National Marrow Donor Program, we can sometimes even have a greater chance of finding a match on that registry. As of our last check, around 24 million people have volunteered for Be The Match, meaning that they have submitted their cheek swab and that they are willing to donate their stem cells if someone who matches them is in need. And so first we look at siblings typically, and if we don't find a match with the siblings, then we'll go to the National Marrow Donor Program and perform a donor search from there.

If we don't find a match within the National Marrow Donor Program, then we can consider additional sources of stem cells. We sometimes refer to these as alternative donors, meaning they may not have complete matches. We can, for example, sometimes acquire stem cells from a healthy parent if they're healthy enough to

donate or an adult child they can also donate for their parent. This type of transplant is, by definition, mismatched though, and so we tend to refer to this type of transplant as haploidentical or a half-match, meaning that they are just a half-match and not a complete match.

As you could imagine, there might be some additional risks to this. Potentially more immune suppression has to be used because of that mismatch to overcome the engraftment barrier, so it could be that the immune system takes a little bit longer to recover with this type of transplant, but it's a very good option if someone does not have a full match.

And then, finally, we can also use partially mismatched unrelated donors, and we can also use cord blood. Cord blood is a source of hematopoietic stem cells that comes from the umbilical cord, so after a mom has a baby, she can, at some hospitals, donate the umbilical cord and the placenta and stem cells can be taken from there and stored, cryopreserved for future use.

So, with all of those options being family members, the National Marrow Donor Program, half-matched parents or children, mismatched unrelated donors and core blood, nowadays the vast majority of patients who are in need of a transplant will have an adequate donor.

Christina: As many of our older patients already know, not everybody does qualify for a stem cell transplant. Can you tell us what makes a patient a good candidate for transplant and why is age a factor?

Dr. Holtan: Absolutely. So, a lot of thought goes into preparing for and planning for a transplant. It's still a really intense undertaking and so we want to make sure that we have all of the factors optimized to make the outcome as successful as possible.

I talk about this like preparing a plane for takeoff when I'm talking to patients and their families about the preparations for this. A lot of planning goes into the procedure

before you actually go down the runway and take off. We need to know that the underlying disease or the reason for the transplant is well controlled. Trying to do a transplant where the cancer or underlying condition is really uncontrolled can make the transplant a lot more difficult. And so ideally the primary disease is controlled, maybe even in complete remission where we can't detect the cancer at all at the time of transplant, that can be quite ideal.

Another thing we need to find a donor, as we had just discussed. And then going from there, we really want to optimize as much as we can about the patient's health in preparation for a transplant. We do extensive testing to make sure that the heart can withstand the chemotherapy and radiation that may be involved, that the lungs are healthy, that the kidneys and liver are in good condition. We want to know that we have the ability to go through these procedures and have the vital organs remain healthy.

We also want any potential infections controlled as much as possible. With a transplant of any type, essentially, we're replacing the immune system from scratch, and so we don't want to go into a transplant, if at all possible, with any uncontrolled infections because that infection will be more difficult to get over.

Now you mentioned age. Age is one factor, but even more so is really muscle mass. Some of our recent research and efforts are going into better supporting transplant patients through the process. We're really focusing more and more on improving muscle mass and that will help resilient to the transplant. Even though there may not be any surgery, or any scars related to this, it's every bit as intense as open-heart surgery or some other major surgery where there's a lot of recovery that's necessary. And so, the more muscle mass that someone comes to us for a transplant, the easier it will be to overcome the side effects from the conditioning regimen and all the medications and the low blood counts that will ensue.

And then, finally, another really critical piece, in addition to making sure that the body is healthy for a transplant, is to make sure that the mind is healthy as well and that someone has adequate social support to make it through this grueling procedure. There's a lot of visits, a lot of physician evaluations, a lot of interventions with nursing, a lot of time spent in infusion, a lot of time spent in the hospital. It's really critical for the success of the transplant for someone to be well supported to really have a good support network to make it through all of the challenges that they will face as they recover.

Elissa: So, you mentioned a lot of challenges the patients are going to be facing. Patients that are looking into a potential transplant right now that might be listening have concerns, we'll talk about side effects in a little bit, but one of those things they're thinking about is cost. Is transplant something that's covered by insurance, and what could be the potential financial burden for patients?

Dr. Holtan: Yeah. That is absolutely first and foremost on a lot of people's minds. The transplant itself should be covered by insurance. Usually when we're talking about doing these transplants, they're not experimental. This is something that would be standard of care and should be covered.

But there are pieces that may have added burden or have various coverage that might need to be considered. One of those burdens is the potential need for relocation. Not every city, and sometimes not even every state, has a transplant center and so it might be necessary for a patient and family to completely relocate to a new city in order to receive their transplant. And, certainly, that is a significant financial burden for some.

At Minnesota, the way that we try to address this is that we are fortunate to work with the American Cancer Society and have a Hope Lodge where people can stay for a very, very low cost, but other centers may have different housing options that are available

to families. So, I think that is one main financial burden that patients and families can face.

Another one is the cost of medications, and this is highly variable between different insurance plans. The supportive medications that we use can be very expensive. From the antinausea medicines, to antibiotics, antifungal medicines, treatment and prevention of graft-versus-host disease and those medications, those can all really add up. That's one of those pieces that has to be investigated on a case-by-case basis because coverage will certainly differ widely for different individuals for those medications.

Christina: Thank you. I would love to talk about what happens after transplant. There are two major milestones that usually happen at 100 days and at 1 year post transplant. Can you talk about the implications for these milestones and what precautions need to be taken?

Dr. Holtan: Yeah, that's right. There are two main milestones posttransplant that we think of in terms of the timing, 100 days and 1 year. The first 100 days are about getting the new immune system established. The way that we kind of break this down, the first part of the transplant is the conditioning, which will be chemotherapy and/or radiation, and that's designed to suppress the patient's immune system and make way for the new cells so that they can come into the bone marrow and engraft.

The way that I describe this for patients I think about this like trying to prepare for planting a garden. There may be some weeds that you need to get rid of. There may just need to be a clearing made so that you can make a nice bed for the new seeds to go into so that they can start to grow and be strong and healthy. So, the conditioning is like getting the ground ready for the new stem cells.

When we give the stem cell infusion, that's given just like a blood transfusion. That's like planting the seeds. Once we give those stem cells through usually something called a Hickman catheter or some kind of line that allows the intravenous

administration of those stem cells, they will circulate around the body, but they'll find their new home within the bone marrow within just a few hours. So that's like planting the seeds in the ground and from there we just have to wait for those seeds to grow. So when you plant new seeds in a garden, you have to water them, you have to prevent invaders from pests and keep those seeds protected so that they can grow up and be healthy. Similarly, we are protecting patients, keeping them free from infections, giving them the support, they need to let those stem cells grow.

So, the next couple of weeks are the time in which the seeds start to grow, and we start to see evidence of the stem cells engrafting. We can tell that by looking at the blood counts. Usually, the blood counts go quite low after the conditioning process but then they'll start to come back up and that shows us that those seeds are starting to develop into a new healthy immune system. The amount of time that takes varies widely depending upon the number of stem cells we transplanted, the intensity of the conditioning, and a number of other patient-and-donor-specific factors. But, in general, after about I would say on average two to three weeks, we're seeing the stem cells start to grow and we're seeing improvement in the blood counts.

Once we see that improvement, we're able to have patients usually leave the hospital. Or if they're outpatients the entire time, which we can do in some circumstances, we're starting to see patients less frequently, give them a little bit of more time at home to recover but watching really carefully through 100 days to make sure those seeds are really growing well, that the blood counts are improving, that the new immune system is getting established.

At day 100, we expect to see blood counts be close to normal, although some people may still have some anemia or low hemoglobin for a time or maybe slightly low platelets as well, but we expect to see close to normal blood counts and that people are starting to feel stronger and feel more like themselves.

What I typically recommend is after day 100, if people feel well enough and strong enough after an autologous transplant, they can return to work at that time. But I usually have people start part time and gradually build back up. However, after an allogeneic transplant using someone else's stem cells, I typically recommend that people stay off work for six months just to give even more time for that new immune system to take hold and for additional recovery so that people are really feeling good by the time they head back to work.

Between day 100 and 1 year, people will come back to the transplant center for periodic evaluations and management of any conditions as they might emerge; for example, infections or graft-versus-host disease. Otherwise, the next big milestone would be the evaluation that we do at 1-year posttransplant. This typically involves a head-to-toe look to see how the patient is recovering. We're usually doing some kind of test to establish if the cancer or other condition for which people were transplanted remains controlled. Often this will be a bone marrow biopsy or CT scans or a PET scan. But then we're also looking to see how the immune system has recovered.

We can look at specific subsets of lymphocytes to make sure that the lymphocytes are maturing as we expect them to. We can look at something called immunoglobulins to make sure that the immune system is producing the antibodies it needs to prevent infections. And that really gives us a good sense of how the immune system is functioning at one-year posttransplant. What we hope to see is that the immune function is, hopefully, pretty close to normal at one-year posttransplant.

What we then do is proceed to repeat childhood vaccinations at one year. Other centers might revaccinate their transplant recipients earlier. I think there are a variety of different protocols for this out there, but at our center, and several others, what we do is we wait until someone is at one-year posttransplant to renew or redo their vaccine series.

So why do we do this? With a transplant, as I had mentioned, you're essentially completely replacing your immune system from scratch. You're starting entirely over and any immunologic memory that was there from prior vaccinations or prior infections that's really gone. It's now time to re-educate the immune system and help prepare to fight even more infections. So, beginning at one-year posttransplant, we begin our posttransplant vaccine series, and that is a series of boosters that will actually go all the way through just a little bit beyond two years posttransplant in order to redo all of the childhood vaccines that a person needs.

Elissa: Wow! Now with all the treatments for cancer, patients often worry about side effects after a procedure like this. So, what are the potential side effects of a stem cell transplant?

Dr. Holtan: Yeah. It's a great question and it's a complicated one to answer. It varies greatly based upon the underlying disease and how we are performing the transplant. In particular the side effects will vary by the conditioning. And that's the chemotherapy or the radiation that's used prior to the stem cell treatment or transplant. So, most of the side effects that we endure are really related to the conditioning regimen at least in the early weeks posttransplant.

Some side effects that are pretty universal, most people will lose their hair, but this is temporary, but that definitely occurs for the majority of patients starting around two to three weeks posttransplant. Also, blood counts go low and so what that means is most people will need some kind of transfusion support, either red blood cells or platelets or both, to help make it through. Most people will have fevers. Many will have identifiable infections. Many people will have loss of appetite, mouth sores, diarrhea. These are all, again, side effects of the conditioning regimen.

Most of these side effects are significantly improving, if not completely resolved by two, three, four weeks posttransplant. Sometimes the appetite takes a little bit longer, but that usually does come back within a few weeks posttransplant as well.

After the blood counts have come back in, then we're looking at some additional potential risks. We can still have later infections. These are infections that are typically from viruses that are already within us. So, we come to transplant knowing that people have had exposures to viruses such as cytomegalovirus or Epstein-Barr virus. Sometimes these viruses will reactivate when the immune system is low, and we'll have to treat those. And so, we watch for that in that intermediate recovery period posttransplant.

I should mention graft-versus-host disease as well. This was the whole reason I got interested in transplant is it's possible for the donor T-cells or one of the immune cell subsets to recognize normal, healthy tissues in the recipient and attack them. The average time that this comes on posttransplant is between 30 and 60 days posttransplant, and this is really only a risk with allogeneic transplant. So, this is only something that we see typically if someone is getting a transplant from a donor. It would be unusual, not impossible, but unusual to have this after an autologous transplant.

So, graft-versus-host disease, again, around day 30 to 60 posttransplant. Most of the time, this is a skin rash and most of the time we can treat it just with topical creams. Sometimes we might need to give additional immune suppression, though, if it starts to become a severe skin rash or involve internal organs causing nausea, vomiting, diarrhea, or elevated liver function tests.

Elissa: Could it develop later than the 60 days?

Dr. Holtan: Good question. So acute GVHD typically comes on pretty early between day 30 and day 60. More commonly in reduced intensity or nonmyeloablative transplants, late acute GVHD can occur around day 100, even through day 180. But long term, long after the acute toxicities have resolved, it is possible to develop chronic graft versus host disease. So, I just want to spend a little bit of time differentiating these.

Acute graft-versus-host disease comes on typically within the first few weeks to month posttransplant. It's caused by those donor T-cells that are recognizing the skin, intestinal tract, or liver. And we recognize this, and we want people to be at the transplant center so that we can treat it immediately. If it's not treated quickly, it can become life-threatening, and so that's the reason we're watching people so carefully early posttransplant.

Now later posttransplant, chronic graft-versus-host disease can develop. This is something that usually shows symptoms developing months to years after the transplant and looks a bit more like immune disorders such as scleroderma or rheumatoid arthritis. People can get tightening of their skin, sometimes a skin rash, tightening of their joints and muscles, dry eyes, dry mouth, problems with cough or breathing issues, less commonly intestinal side effects, less commonly liver problems as well. Chronic graft-versus-host disease can take a lot of different manifestations and that's why we do recommend still continuing to see people from the transplant center even long term to screen for these late effects because sometimes the changes can be quite subtle and if they're not picked up, can lead to permanent scarring or long-term chronic graft-versus-host disease that needs a long duration of treatment.

So, there's acute and chronic graft-versus-host disease. They look different. They have different risks. They're both manageable, but the goal of treatment of acute GVHD is completely getting rid of it. The goal of treatment for chronic GVHD is trying to avoid it. And if it does happen, treat it as early as possible to minimize the risk of long-term or severe damage.

Elissa: Now what is the risk of GVHD from a twin donor, like you had mentioned earlier?

Dr. Holtan: Yeah, that's a great question. It's almost zero.

Elissa: Wow.

Dr. Holtan: So, I can't say it's totally zero.

Elissa: Yeah.

Dr. Holtan: And this is still true for an autologous transplant. We can rarely have the new immune system, even though it comes from yourself, even though it's identical, we can still sometimes get graft-versus-host disease-like symptoms after a twin transplant or an autotransplant; it's just quite rare.

Elissa: Last question about these side effects. Is there risk of infertility after transplant?

Dr. Holtan: Yup, definitely. So, I wanted to just touch on some late effects as well and that's certainly one of them. We can see infertility. The intensity of the chemotherapy and radiation that's required can lead to ovarian failure, premature ovarian failure in females and cessation of sperm production in males. It's absolutely possible for this to occur and so we do recommend, if it's feasible, for someone to see a fertility specialist prior to transplant and, hopefully, do cryopreservation if that's an option or looking at other types of options prior to transplant. Because you're right, once we embark on this intensive therapy, there's a high risk of infertility. I certainly have seen patients have children after the transplant, but it's uncommon and significantly higher risk. So that is absolutely one of the concerns for sure.

Speaking of long-term potential side effects, there's a long-term risk of accelerated cardiovascular disease and accelerated aging. For that reason, we really want people to be tied into a primary care doctor managing their blood pressure, managing their cholesterol, and mitigating every risk for cardiovascular disease, including not smoking, making sure their diet's good, paying attention to exercise and all that.

Everything that's recommended for any individual to prevent heart disease is that much more important in someone who's been through a transplant because we do know that chemotherapy and radiation can accelerate those biologic processes. It's

something that we want to be managing and be very much aware of and try to help people live the healthiest lives possible after a transplant.

Christina: I know that a big part of your research is focusing on reducing the effects of graft-versus-host disease. Can you tell us a little bit more about your research and what makes you really excited about this area of research?

Dr. Holtan: Absolutely. Graft-versus-host disease prevention and treatment has changed so much in the past few years, and it's been just amazing to see. We used to say that somewhere around 30 to 50% of patients could get acute graft-versus-host disease and that even up to 75% of people could get chronic graft-versus-host disease.

This is based upon the way that we prevented GVHD going back to the 1980s. The gold standard, as we say, has been using a combination of two drugs. One is a calcineurin inhibitor such as tacrolimus or cyclosporin, and the other is methotrexate. Since the '80s, we've been using two drugs to prevent graft-versus-host disease. And even with a perfect match, those were the rates of graft-versus-host disease that we were getting. It was still a significant burden.

We're making some significant headway in clinical trials right now and it will, I guess, remain to be seen, hopefully in the next few months, whether we'll have a new standard of care. So specifically, there's a Phase III study that's completed, and we expect to know results, hopefully, by the end of the year to know whether a third drug added to this backbone can help reduce graft-versus-host disease risk even more.

What I'm referring to is a concept called posttransplant cyclophosphamide. When investigators around the world studied using chemotherapy after the transplant, they found marked reduction in rates of acute and chronic graft-versus-host disease.

So, let me just back up and explain this a little bit more. It sounds kind of crazy where we give our conditioning but then after the transplant, we give more chemotherapy?

So, we do. What we've done in these studies is we give, cyclophosphamide which is a chemotherapy drug. We've given it on days 3 and 4 after the transplant and we've studied this in both Phase II studies and now with a Phase III study that's pending.

What this does is it really helps reduce those alloreactive T-cells that can cause graft-versus-host disease, but it spares the stem cells. The stem cells have an enzyme that can metabolize the chemotherapy drug so they're unaffected, but those graft-versus-host disease-causing cells can be eliminated very effectively using that posttransplant cyclophosphamide.

The studies that we're waiting for will be comparing two drugs, which was our old standard, to this new platform where we use posttransplant cyclophosphamide and, in addition, use tacrolimus and mycophenolate, so a three-drug GVHD prophylaxis regimen see if that really reduces our risk.

I can just say that in our Phase II setting, we've seen just really striking reductions in acute and chronic graft-versus-host disease incidents and severity, and so we're really excited to see if this will pan out in a Phase III setting.

Clinical trials are so important to help us advance patient care and advance all the things that we do to try to make the transplant more safe and more effective. A Phase I study is where we're testing to see if a new drug is safe. Phase II we're looking to see some signs that it works. Is it efficacious? In Phase III, we're comparing it a drug to an established standard to say, "Is it actually better than the current way that we practice?" And we really do need all three phases to make significant advancements in the field.

I heard a statistic recently that somewhere around 10% or fewer of patients who are going through transplants right now are participating in clinical trials or have options available to them. I certainly would encourage those who are going through a transplant or considering it to think about clinical trials. We would never ask someone to sign up for a treatment that we think would ever be inferior. What we're always

doing is that careful process, as I've mentioned, going from is the medication safe, is it effective, is it even better than the gold standard? We do that in a very thoughtful, careful process and would really hope that we could have good conversations about the potential risks, alternatives, benefits of clinical trials.

At Minnesota we do a lot of research, and a lot of the platforms that have been developed for transplant have really been tested and developed here. We have a big legacy of clinical research in transplant at the University of Minnesota, and so it's definitely a part of our culture. It's just so important to the field.

Elissa: I'm so glad that you brought up clinical trials because it really is just so important for patients to look into the clinical trials. It benefits them and they can have access to those newer therapies. So, speaking of newer therapies, with some newer therapies being available, such as CAR T-cell therapy or immunotherapies, what do we see for the future with stem cell transplants? Are there any new clinical trials or new diagnoses that could benefit from transplant?

Dr. Holtan: That's a great question. I think that the field will just continue to expand, both in our ability to more safely perform transplants and cellular therapies, as well as the indications. It's just going to continue to grow. It's something that's so overwhelming it's hard to even put my mind around fully. But we are now basically able to take someone's immune cells and genetically modify them to be cancer fighters and give them back to patients, something called antigen chimeric receptor or CAR T-cell therapy. That's available for a lot of patients, but there are some diseases for which we have not yet developed or proven effective CAR T-cell therapies. I think that will continue to evolve. It's available now for a lot of B-cell malignancies, B-cell leukemias, B-cell lymphomas but under development now for acute myeloid leukemia and even solid tumors. So, stay tuned. I think that field is going to continue to develop.

In terms of transplants for additional indications, I'm really excited by the potential extension of transplant for noncancerous conditions. So, it may be possible to reset the immune system using an autologous transplant if someone has an immune disease such as scleroderma or maybe even inflammatory bowel disease. This has been tested in Phase II studies, and there are some Phase III studies ongoing here as well, looking at that concept of resetting the immune system with an autologous transplant for some of these life-threatening autoimmune diseases.

There are also a number of genetic conditions or metabolic disorders that could be amenable to transplant, and we're investigating this at Minnesota as well as other places as well looking at the possibility of extending transplant to diseases such as adrenoleukodystrophy and other leukoencephalopathies, of course, looking at this for other bone marrow conditions or hemoglobinopathies. I just think that this is essentially a regenerative modality that could have really wide implications for the future.

Elissa: That's great. Now our final question to you, Dr. Holtan, on our patient podcast homepage, we have a quote that says, "After diagnosis comes hope." Based on your research and experience with patients who have received a transplant, what would you say to patients and their families to give them hope if they are considering a transplant or have recently had one?

Dr. Holtan: Absolutely. That's a great question, and there is so much hope. Maybe I could just share a story.

Elissa: Yes.

Dr. Holtan: As I've been focused on transplant for almost 20 years, the field has changed for the better so much. It was always a difficult treatment. I remember seeing patients going through blood and marrow transplant before drugs such as voriconazole were available, before we had effective prevention for CMV

[cytomegalovirus], for example. The field has just improved so much that we can extend this therapy to so many more patients.

When someone is meeting with a transplant physician, I think a lot of times, we tend to focus on the risks. And we do this because we know this is a very intense procedure that does come with a lot of potential side effects but also look at the good. This is a chance to, hopefully, overcome a devastating diagnosis and something that, with modern supportive care and improvements through clinical research, most of our patients do come through this successfully.

So, it's an incredible honor to be able to walk with patients through this journey and to help them through these very, very difficult times. And having seen the progress in our field I can say that it's just going to continue to keep getting better. And what I encourage people to do is to be a part of that continued change. Be a part of the continued growth. Help us make the process even better for the next person.

In my own research, for example, I developed a clinical trial to treat graft-versus-host disease using something that's going to sound a little bit crazy. I had the idea that perhaps I could use the immunobiology of pregnancy to help treat life-threatening graft-versus-host disease. And why would I ever think that? When I was pregnant with my son 15 years ago, I was struck by how amazing it was that the maternal immune system could be modified by the hormones in pregnancy to not attack the fetus. And I thought this immunobiology of pregnancy could potentially help us treat graft-versus-host disease.

I developed this concept where I would use pregnancy hormones, and this is a drug that's been around for 50 plus years. It's a inexpensive easy-to-obtain pregnancy hormone supplement. And I wanted to apply that to treat life-threatening graft-versus-host disease.

And when I would tell patients about the idea that I had when I was pregnant and how this could potentially impact their care, most of the time patients looked at me

and said, "That makes so much sense. We should do it." Someone helped to give you that idea and someone helped me be where I am today. I want to help, if this will help potentially change medicine or open new avenues for patients, I want to be a part of that story.

That was so amazing to hear people really wanting to be a part of that and trusting us and we wanted to give back as much as possible. Telling patients our results and sharing with them as much as we could along the way. Then when we're able to give our presentations, thanking them for their participation in helping us change how we approach some of these difficult diseases.

It was funny. Some of the women who I would be treating, or the wives of the patients I might be treating would say, "Well, of course, this just makes sense." So, it was neat to see some people have the lightbulb go off.

We can get inspiration from anywhere. I've gotten inspiration from my kids. I get inspiration from my patients. Not all progress is something that has to be done in a laboratory, and we can get inspiration and ideas from literally anywhere.

And so, my hope is that people feel engaged and free to come up with their own ideas and share them and be a part of continuing to move this field forward. A lot of people have been here before you and have given what they've had to improve outcomes. Now the questions are even more difficult, but we have so many great ideas and so many new avenues to improve. I just think that the field will continue to be revolutionized with continued engagement between patients, families, and their physicians.

Elissa: I love that. What a neat story and an incredible innovative idea. I hope that it is continuing to show progress.

Thank you so much, Dr. Holtan, and, of course, our guest cohost, Christina, for joining us today and talking all things transplant. I hope that our patients and caregivers who

are listening to this, either considering a transplant or have had one that they have learned a lot and can find hope in that there are so many good things coming for transplant and for other treatments. So, thank you, again, both so much for being here with us today.

Dr. Holtan: Thank you so much. I really appreciated this opportunity.

Christina: Thank you.

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.

To help us continue to provide the engaging content for all people affected by cancer, we would like to ask you to complete a brief survey that can be found in the show notes or at TheBloodline.org. This is your opportunity to provide feedback and suggested topics that will help so many people. We would also like to know about you and how we can serve you better. The survey is completely anonymous and no identifying information will be taken. 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.

Have you or a loved one been affected by a blood cancer? LLS has many resources available to you – financial support, peer-to-peer connection, nutritional support, and more. We encourage patients and caregivers to contact our Information Specialists at 1-800-955-4572 or go to LLS.org/PatientSupport. You can also find more information about stem cell transplants at LLS.org/SCT. All of these links will be found in the show notes or at TheBloodline.org.

Thank you again for listening. Be sure to subscribe to *The Bloodline* so you don't miss an episode. We look forward to having you join us next time.