LEUKEMIA & LYMPHOMA SOCIETY®

THE BLOODLINE WITH LLS

A PODCAST FOR PATIENTS AND CAREGIVERS

Episode: 'Patient-Doctor Perspectives: Adult Acute Lymphoblastic Leukemia (ALL)'

Description:

Tune in to the latest episode of the *Patient-Doctor Perspectives* series, featuring an enlightening conversation with Dr. Judith Shizuru of Stanford Medicine and acute lymphoblastic leukemia (ALL) survivor, Peter Feinberg. Delve into the world of cutting-edge ALL treatments and gain insight from a patient who shares his personal story of treatments, bone marrow transplantation and re-vaccination challenges.

Transcript:

Elissa: Welcome to *The Bloodline with LLS*.

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

Elissa: Today, we will be speaking with Peter Feinberg and Dr. Judith Shizuru. Peter is an acute lymphoblastic leukemia, or ALL, survivor and a corporate and commercial attorney. He was diagnosed in December of 2020, nearly two years from his first abnormal blood test, and seven months after symptoms started. After chemotherapy and a bone marrow transplant in April of 2021, he reached remission. While he has gratefully stayed in remission, he has continued to grapple with the emotional and physical effects of cancer, including challenges with re-vaccination post-transplant.

Dr. Shizuru is a Professor of Medicine and of Pediatrics at the Stanford University School of Medicine in Palo Alto, California, where she is a member of the Blood and Marrow Transplantation faculty, the Stanford Immunology Program, and the Institute of Stem Cell Biology and Regenerative Medicine. Her clinical and research efforts are focused on improving the safety and efficacy of stem cell transplantation, which is the most widely practiced and powerful form of cellular therapy.

In this episode of our Patient-Doctor Perspective series, we will be discussing the latest advances and treatments for acute lymphoblastic leukemia and the experiences of one patient through treatments and the challenges that followed.

Welcome Peter and Dr. Shizuru.

Peter Feinberg: Thank you.

Judith Anne Shizuru, MD: Thank you.

Elissa: So, we'll start with Dr. Shizuru. Our main focus today is on acute lymphoblastic leukemia, or ALL. Could you explain to our listeners what that is?

Dr. Shizuru: Sure. Acute lymphoblastic leukemia is a cancer of immature bone marrow cells. And so, the bone marrow, of course, is where blood is made, and it's a very busy place where blood's being made all the time. It's like a community where the blood cell lineages are being produced, the platelets, the red cells, and the white blood cells.

What happens in leukemia is that one of the immature cells gets a DNA mutation and that mutation then results in the production of proteins that then drive that cell to behave abnormally, so it drives the cells to proliferate, or divide, a lot more than they should and then ignore the signals that are coming from the microenvironment to stop dividing. And also, they're supposed to differentiate but it stops the cells from differentiating. So, what you get in ALL is the abnormal proliferation of cells that are growing rapidly, taking over the space in the bone marrow and suppressing the development of the other blood cells.

Margie: Thank you for that explanation, doctor. Now, Peter, in 2020, you were diagnosed with ALL. That's nearly two years after your first concerning blood test. Can you please let us know what was it that led you to this diagnosis and if you had any symptoms?

Peter: It's a great question, Margie. I had had a bad body surfing accident in the spring of 2019 which resulted in a broken neck, broken ribs on my left side, a punctured lung, and various other different things. And as a result of that, I had several rounds of blood tests which showed low red blood cell counts and low platelets. As I healed, the counts got somewhat closer to normal but never really fully came back to normal.

My doctor kept retaking these tests, but she had not really discussed with me what the consequences might be if the numbers were truly off. Her belief was that they were off somewhat because I had never had problems in the past, these are the trauma that my body had suffered. Rather than discuss what other tests might be done or even coming back and retesting in six months, it just ended up getting put to the side. And that seemed okay at the time because once the body surfing injuries healed, I felt otherwise fine.

I fast forward from that almost a year to about the start of the pandemic, and one of the things that I think has helped in my recovery, also helped with my diagnostics, is the fact that I have over the course of my life been very physically fit and had very vigorous workouts. And I've been a lifelong runner, and my times in running started dropping from sub seven-minute miles to nine-minute plus miles almost overnight. And even more worrisome at the end of my runs, I felt like I needed supplemental oxygen. And I had made a comment to my sister, "Boy, getting old sure stinks." And she said, "Well what do you mean?" And I said, "You know, my running times have fallen off a cliff." And she said, "Well you're right that getting old does stink, but those are too drastic changes to have happen that quickly."

As I said, this was during the pandemic, and I think everybody was sort of obsessed with COVID, and I was having a very busy year workwise, so it ended up getting kind of kicked sideways until I finally got my annual physical that year about five or six months after that, at which point in time my reds and my platelets were even worse

than they had been. And I said to my doctor, "I'm going to stay in your office until we find out what the problem is here."

And this started a barrage of tests. And I was quite shocked because, as I said, there really had not been discussion if the low numbers were correct numbers what that meant, but my assumption was that what it meant was that I had low to medium grade anemia and I was going to be told I needed to come into the doctor's office a few times a year to get a shot of B12. But I immediately got an endoscope and a colonoscopy. When I asked my doctor why, she said, "Well we're looking for esophageal and colon and pancreatic cancer," which was quite jolting because I really had no idea that that would be the first thing that they'd look at.

After going through those things and finding that that wasn't the case, there was a lot of heart work, as you might imagine, because of the level of exhaustion and fatigue that I was feeling at that stage; and that all proved to be fine. I had been reading a lot about long-haul COVID cases which seemed to have some of the same symptoms as I was having, and I had also been spending a lot of time with my college roommate, who was diagnosed with multiple myeloma, so that was on my mind.

But as we started going through these things and eliminating possibilities, one of the things that jumped out to me was that perhaps this could be leukemia since that had been what had ultimately killed my mom and her mom. And they did a test, which showed a 90% likelihood that I would have either lymphoma or some form of leukemia with a 10% likelihood that I would have an equally insidious but rare blood disease. And I was actually kind of told at that point that to whatever extent I could root for anything, I should be rooting for a chronic form of leukemia that might be treatable through pills. And the thought was that because I had been living with this presumably for an extended period of time with relatively minor symptoms that was probably what I had.

That was followed up eventually with a bone marrow biopsy, which showed that what I had was B cell ALL, at which point in time I got a call from my primary medical provider, telling me that if I was not in the hospital within 36 hours that they basically could not be responsible for whether I lived or died. So, the whole process was rather jolting and surprising.

Elissa: Wow! Now let's go back for a moment. You mentioned that your mother and your grandmother had leukemia. That seems very surprising. Could you tell us a little bit more about that?

Peter: Yeah, absolutely. My mom's mom died when I was eight, and she was an incredibly vigorous woman. She was 60 years old, and I have no idea when she was diagnosed or what kind of leukemia she had.

We had had a party for her 60th birthday at her house about three weeks before she died but at that point she had very bad shingles. It made a big impression on me as a child. She had a bandage over her eye, and she had sort of large lesions everywhere; but in terms of her energy level, she seemed no different than she ever did.

About three weeks after that party, she died. I certainly had not heard the word leukemia prior to that party. I'm not sure I ever heard the word leukemia in my life, as an eight-year-old. But somewhere around the time she died it was mentioned to me that she had died of leukemia.

Probably right around that time, my mom was diagnosed with leukemia. And I believe that my mom would've been about 36 years old. It took about six or seven years afterwards before my mom shared with my sister and I the fact that she had been diagnosed with leukemia. I am imagining with, where the treatment universe was with leukemia at that point, that it must have been a chronic form rather than an acute form, as she lived so long with it. She was right up until the end really never hospitalized with it either, which I think she probably would have been had it been an acute form.

And my mom lived her life so fully. She was a learning disabilities consultant for a school system. And on the last day on the planet, she was conscious she went in, taught a full day of school, and drove herself an hour and a half to the hospital where her attending physician was. We had no particular sense that the end was near. And that was actually very consistent, in a sense, with my experience because while I was feeling some fatigue and some breathlessness when I exercised very physically, if you had seen me otherwise, and this has been sort of a recurring theme both during my diagnostic and treatment periods, you would not have really noticed anything was wrong.

So it all took us very much by surprise. The trend was going in the wrong direction because her mom was 60 when she died, my mom was 49 when she died, so I've already outlived both of them thanks to great researchers like Dr. Shizuru and her colleagues and LLS who have come up with such wonderful protocols in the intervening years. It's, obviously, something I have a lot of mixed feelings about because I wish that both of them had been able to have availed themselves of the advances in treatment that have come about since the time of their deaths.

Elissa: Absolutely.

Margie: Understandably so. Well, thank you for giving us the backstory.

Doctor, is that common for there to be a family history of leukemia? Peter mentioned cytogenic testing. Would this family history of leukemia be because of genetics, environment, or a combination of both?

Dr. Shizuru: In Peter's case, it is unusual. Generally, we think of leukemia as being those mutations that I talked about that drive the leukemia as arising spontaneously. In the case of ALL, it's probably 5% or less where there is a genetic predisposition. In looking at Peter's case, we specifically were thinking that he was going to need a transplant. So, we wanted to interrogate any possible donors, which was his sister, who actually turned out to be an HLA (Human Leukocyte Antigen) match. And we did

do a fairly extensive panel, the ones that now have been developed to pick up mutations that could be problematic; and, in her case, it was negative. But I do want to emphasize that there are certain mutations that can predispose family members to have leukemia. We did not pick that up in his case and importantly in the case of his donor.

Peter: But, a lot of that testing is still relatively preliminary, am I right about that, Dr. Shizuru, as compared to say the BRCA gene where it's much more causally connected?

Dr. Shizuru: Right. I think that this is an emerging part of understanding the biology of leukemias, to really be able to find the technologies to identify the mutation. Even though we feel we have a lot more mutations than we have the opportunity to look at, you have to still discover more mutations that will be driving the leukemia process. So, I think as time goes on, we will find more and more of those driver mutations and ways to pick them up so that we can screen people in advance.

Elissa: Yeah. Now, if you are able to screen people in advance and get more of this genetic testing to show a predisposition, is there anything that you can do to prevent the leukemia or prepare for that?

Dr. Shizuru: That's a great question. I think that along with this technology, there's a whole field that is called CHIP, which is clonal hematopoiesis of indeterminant prognosis [potential], where a large segment of people were screened and there were mutations that were picked up. And if you follow those individuals for a long period of time, some of those mutations that we think can potentially problematic don't amount to anything whereas some others do result, for example, in myelodysplastic syndromes (MDS).

As we understand what our technology tells us, we have to also make the correlation between what we see clinically and then what we're picking up in terms of these assays. So, the answer to your question is that if you reach a certain threshold where the mutations are at a level that are concerning, you follow those people more closely.

Elissa: Yes.

Dr. Shizuru: But certainly, in the case of a donor, I think that that would be a red flag. If we have the opportunity to use a different donor, then we would opt for that at this point.

Peter: And on my side, that gave an even more poignant aspect because not only could it potentially have precluded my sister as being my donor, but she might've been in a situation where she was dealing with being a potential leukemia patient in the future. So, the two of us spent a lot of time talking about that, as you might imagine, while this was going on.

Elissa: Absolutely. Now, Peter, let's discuss your treatment since you just talked about having a donor. So, what were the treatments that you had after your diagnosis?

Peter: So, after I was given that 36 hours or else ultimatum, I did actually manage to negotiate it out to about four and a half days and I spoke to a former colleague of Dr. Shizuru's, who's at UCSF (University of California, San Francisco), to get a second opinion because I had been very plugged into the blood cancer group at UCSF through following around my college roommate, as I mentioned, who had MM (multiple myeloma). At that point in time there was one approved first-line treatment protocol for B cell ALL which was hyper-CVAD. It comes in either two rounds or one round with two stages. The first one was the longer round, and I absolutely sailed through it. I really had no bad side effects as I went through it.

After the second round of CVAD, I felt like I had been run over by a steam roller. I had lesions all over my body. I was running a high fever. I had horrible headaches. All sorts of different problems. And then on top of that, that's when they sort of do your first recheck on the bone marrow biopsy. My initial diagnosis indicated that I had 15% spikes of cancer in my bone marrow. After these two-part rounds of hyper-CVAD, I had gone from 15% to 50%. After getting that news, that was really the first

time that I started thinking seriously that this might kill me, and that was rather overwhelming. I will always have a very special place in my heart for both Dr. Shizuru and her colleague at UCSF because they were both very calming to me at that point. That was the first time I had met Dr. Shizuru. She was very confident, as was her colleague at UCSF, that this next stage of treatment was going to be what got me to a point where I was going to be able to get a bone marrow transplant at that stage.

Fortunately, in the last decade or so, a treatment is out there, which I believe has recently been now approved as a first-line treatment, which is a monoclonal antibody called Blincyto® or (blinatumomab). And there's a second one as well that's also approved. It's a 28-day cycle, the first 11 days of which for me were in the hospital. And the induction on that caused fairly horrible fever and headaches in me, which my nurses and practitioners were very helpful in telling me was actually a good sign that it was working. And it flattened out. And then after the end of that 11 days, they significantly up the dosage, which can potentially lead to what they call cytokine release syndrome (CRS), which was not a problem that I had.

And then, they let you go home with something that looks like a Sony Walkman® that basically gets the blin (blinatumomab) into your system, but you can otherwise lead your normal life; and I was feeling absolutely great at that point in time. I had a subsequent bone marrow biopsy. We're up to three at this point. I've lost count of where we are now, but this was the first one that actually looked good. My practitioner, he had prepared me for the fact that he didn't think this would get me to the point yet where I would be ready for a bone marrow transplant but that I should expect that it would get the number down from 50%. And he seemed pleasantly shocked that I was at zero at that point. So-

Elissa: That's great.

Peter: -all of a sudden, the question was do I want to go into the hospital and do the transplant then or did I want to do more blin or how did this want to work? I had met

several people in the hospital, as I was going through this, who had gotten to MRD (minimal/measurable residual disease) zero, no signs of detectable leukemia, and had chosen not to get a transplant immediately and the leukemia came back. I was scared to death that that could happen and that I might not get back to zero again. So, my thought was let's get in and get this done as soon as possible at that stage.

My sister reached out to a practitioner at MD Anderson who was doing some really interesting research on Blincyto and he had actually spoken to me about the fact that he had trials going on at that point with people taking nothing but Blincyto and I think his number was 80% had stayed clear of leukemia for five years after he had started that.

Elissa: Wow!

Peter: And that was a trial that was not approved at that point. It's my understanding that that now is being approved as an alternative to a bone marrow transplant for certain B cell ALL people. And, obviously, if you can find a way to do that, if that is in fact correct, it is probably a lot easier on the body than going through transplant. At that point in time, I was set on the fact that I was going through transplant. I had this great transplant team at Stanford that was ready and waiting for me and that sort of seemed like the course.

Margie: Doctor, for our listeners, can you explain what is transplantation? We know that there are different kinds. What would you tend to utilize on ALL patients?

Dr. Shizuru: Yes. So, there are different kinds of transplants. There's the kind where you get really strong chemotherapy or radiation and then get your own cells returned back. But in the case of ALL, as we talked about, the immature cells that are taking over the bone marrow really need to be replaced and that is what an allogeneic transplant is. So that's a transplant from a donor.

The idea with an allogenic transplant is you want to wipe out, as much as you can, the patient's own blood-forming stem cells and the leukemia along with it, and then replace those recipient cells with cells from the donor. So then you have healthy donor cells there that make blood normally take over the space where those leukemia cells were and then you're also able to leverage the fact that, not only are you transferring the blood-forming machinery of the cells, but you're also transferring in the immune cells of the donor. So, you get this immunotherapeutic benefit. And we think that those immune cells, the healthy lymphocytes from the donor, see the leukemia and can suppress it so you get both wiping out the leukemic clone as much as you can, and you get the cellular benefit of putting in a healthy blood system and then the immunotherapy from the T cells and the lymphocytes.

Elissa: We've also heard these two terms, stem cell transplant and bone marrow transplant. I think a lot of people use them interchangeably, but there are differences between those two, correct?

Dr. Shizuru: Well, there are differences in terms of how you get the stem cells.

Elissa: Okay.

Dr. Shizuru: So, the stem cells live in the bone marrow. They live in specialized niches. Before we knew how to get those stem cells out, we used to take the donors to the operating room and pull the stem cells out of the hip bones. But in the 1980s, people figured out that you can use chemotherapy in some cases and now we know you can use a hormone, the granulocyte colony stimulating factor, GCSF. And what that does is that coaxes those cells in the bone marrow in the donor, the stems cells should divide and then they get released into the bloodstream.

Elissa: Oh!

Dr. Shizuru: And during the time that they're released in the bloodstream, you can collect the blood-forming stem cells in the blood the same way that you collect

platelets from a platelet donor. So, you're getting the same cell population, but actually in the case of the stem cells from the bloodstream, you can get a lot more because it's not just the hip bones that are letting go of their stem cells into the bloodstream but it's all the other bones where the stem cells live.

Elissa: Okay. Before we dive into current ALL treatments, we know there are also protocols for both adults and pediatric patients. What are the differences between those, and should an adult ever receive the pediatric protocol for ALL?

Dr. Shizuru: Yeah. It's important to know that ALL is the most common cancer form in children. It's not in adults. And I think as we learn more about the genetics of what's driving these leukemias, we're seeing that there are differences in the pediatric patients versus the adults. And in the pediatric patients, there are so-called good risk mutations that are more loaded in that population. Those kids get intensive treatments, more intensive than the adults we think can handle. And so, the survival is better in kids that are younger than 15.

There's a whole other patient group between 15 and 39, the adolescent and adult young (AYA) patients that also get the ALL. Their outcomes were not as good; but as time has gone on, those patients have been receiving the intensified pediatric protocols and their outcomes are looking better. But just biologically, it's different in terms of what mutations drive ALL in adults and older adults and what mutations are driving the ALL in children. So, the biology is different and then the approach is different, meaning that the kids can receive more intensive treatment. They receive a drug called L-asparaginase, which is not, for some adults, the drug that they can tolerate. And the treatment is more intense in kids and longer. And so, in terms of getting cures without a transplant, it's higher in those patients.

Elissa: Yeah.

Margie: So, with that said, what are the current treatments for ALL for adults? Is what Peter had a standard treatment?

Dr. Shizuru: Yeah. I think that Peter gave a great summary of really what the standard is. Hyper-CVAD is considered to be frontline. There's five chemotherapies and then there's a steroid, dexamethasone. The chemo will be most effective in rapidly proliferating cells.

And I think that our expectations would have been that Peter would have responded. Especially when he said the spike in his bone marrow, we're looking at the blast numbers in his bone marrow which started out at 15% and concerning after he got that initial chemotherapy that actually went up and so we realized that the chemotherapy wasn't going to work. And as Peter pointed out, it's been really gratifying from both the scientific and medical perspective to see that the technologies that were developed in antibody therapy could then be turned into a drug.

We naturally make antibodies, and they can see molecules on the surface of cells. What we've learned to do is use that technology to target specific molecules on the cells. And the blinatumomab, it's been directed to recognize a molecule that's on the surface of B cell ALL.

What was also done though, in the engineering of that particular molecule, is that it also links another molecule, another antibody receptor site that recognizes T cells, so it brings the T cells into the, to the leukemia cell and those T cells then are activated, and they kill the leukemia cell. It's directed targeting of the cell population against the leukemia cell. And so, this is really a wonderful breakthrough based upon basic immunology work that was done and then protein engineering and then finally to being able to test it in a clinical trial. And it has been shown to be very effective.

I think in Peter's case, you bring the T cell in; and the T cell gets activated, and it makes hormones. And he's right that, when you have activated a lot of T cells and you have a lot of disease, then you're going to have those side effects because the T cells are making hormones that are going to give you fevers and make you feel pretty miserable. So, that's probably what was happening in Peter's case with his first cycle

is his disease burden was pretty high. And so when they used the Blincyto, a lot of T cells were getting activated. I think we were all ecstatic to see when his disease burden went down to zero, nondetectable.

And we would consider, just based upon the fact that he was refractory, that he's high risk, and so we couldn't just say, "Okay, let's see how the blinatumomab alone did." We still look at it as a bridge to transplant. Again, with the transplant concept being that you're going to even more aggressively wipe out every last one of those leukemia cells and the stem cell driver in there and replace that marrow with healthy donor cells.

Peter: And a question I'd like to ask Dr. Shizuru, if I may, on this, just in trying to keep up with what's going on treatment protocols is in addition to Blincyto, it seems like CAR T is now being used for B cell ALL. And it's not really completely clear to me whether that might be as an alternative to a transplant or a conduit to a transplant. I'd love to hear your thoughts on that.

Dr. Shizuru: Well, these are wonderful questions because, really, this is where the field is now. So, rather than relying on the bridge, which is what blinatumomab does, bridging to the leukemia cell and then bringing a T cell in, the CAR T cell has been engineered so that it's a killer cell. It's loaded with the recognition molecule. So, it just goes directly to the target cell.

Also, in the CAR T cells, you've used the patient's own T cells to do the killing. That's the same case in Blincyto, but here you've taken the T cells out, engineered them, and then put them back in.

They've been approved initially for relapse disease and thinking about these things in the future as frontline. So, there's lots of questions about what's the best way to use these agents now? Will they supplant transplant? I don't think we know that. We're going to have to do those studies to be able to determine if that's going to be the case.

To your point with regard to the blinatumomab, MD Anderson has been a big champion of testing these other modes of using these new technologies to forego a transplant. But time will tell.

Peter: And I guess time will tell, is exactly what I was going to ask you because all this stuff has been really going on in the last maybe five to seven years. So long-term survivability data is still not really out there on this. Is that right?

Dr. Shizuru: Exactly. Whereas, we have long-term survival data on transplant, and we know what it can do. But also, I think that the technology is advancing so that we can say, "Look, if you have this genetic abnormality, then transplant still is the way to go versus if you have other mutations, then maybe you potentially could forego a transplant." But, yes, we still have a lot to learn in that regard.

Elissa: These are so many great options for ALL patients. That's just really exciting, and we'll get into some potential new treatments in a bit here.

Peter, let's go back to you for a minute and hear about your life post-transplant. I mentioned in the beginning that you have had some challenges, particularly with your re-vaccination one-year post-transplant. Could you tell us a little bit more about that?

Peter: Sure. The immediate period after transplant, it took a while to really feel the effects of the pre-BMT chemo, probably about five days. But it really flattened me out for about three or four weeks afterwards. I had a lot of fevers.

I had a particularly woeful side effect that I think is relatively common among BMT patients called mucositis, which basically turns all of your mucus membranes, liquifies them so that you have no protection. Your body intensely feels anything that is going on during that point.

And it is a level of pain which as someone who has a very high pain threshold, was almost indescribably bad over the course of several weeks and really was not

successfully treated by almost any of the pain meds. It was somewhat mitigated, but it by no means went away.

After about three or four weeks, that started improving quite quickly. I had a mild to moderate case of skin graft-versus-host disease (GVHD), which took a few rounds with some of Dr. Shizuru's colleagues in the oncological dermatology group at Stanford. They found, eventually, a good treatment and that went away.

And I had had some other problems during that first-year summer, but basically after about the four to five month mark, I started feeling pretty well. And it improved steadily up to the course of my first-year anniversary.

One of the effects of having an allogeneic bone marrow transplant is that you lose all of your childhood immunizations, so that at some point you need to get revaccinated.

Peter: What Stanford had recommended, at least in my case as somebody who's feeling well, was the one-year anniversary, more or less, that I would, over the course of a month, get two to three shots on a once-a-week basis to begin replacing these vaccinations; and that this would happen over the course of several months.

In the first group of shots I had, one was an pneumonia shot and the other was a shingles shot. And I immediately had a fever. I was achy. I was tired. It was about a 72-hour period of feeling really poorly. I had not had a sense that this could be a problem to the extent it was, and after the 72 hours, I started feeling progressively better, but not back to where I had been before I got the shot.

And interestingly, there seems to be a similar series of side effects on all of these things, whether it's leukemia or the treatments, which is sort of fatigue and breathlessness. And I had felt some of this, but my bloodwork continued to look good. I was continuing to present with a very vigorous affect; and to celebrate my one-year anniversary, my wife and I had planned on a one-month trip to Europe.

On the eve of that trip, I had actually not seen any oncologist in person for nine months; and I had had a phone appointment scheduled with my Kaiser oncologist. And I said, "Could I just come in? I'm not feeling badly, but I'm feeling slightly off. I'd like you to put a stethoscope on my chest, take a look at me personally. Just tell me I'm not about to do something really crazy." And she said, "You look great. You sound great. Your energy looks great. Go and have a fantastic trip. But you know what, when you come back, let's get you another one of those pulmonary function tests (PFT)."

There's a battery of tests that you do, because the transplant is such an exhaustive procedure, to make sure that you have the best possible chance of getting through it, and one of them is this pulmonary function test where you do a variety of monitored breathing exercises.

So unlike, say, a blood test, it is a performative test. And for me, it actually showed that despite the fact I had leukemia for a year, that I had chemo, that I had had the Blincyto, I was above 110% of normal in terms of my pulmonary function levels prior to the transplant.

Back to where I was at this one-year period. On the course of the trip, I just felt myself progressively getting more and more tired and weaker, which, of course, person that I am, in no way, shape, or form changed the fact that my wife and I were traveling like two people more your age, Elissa, and much less my age which is probably close to double yours.

I had an appointment with Dr. Shizuru about a week after I got back. I immediately went in to get bloodwork, even before I had the PFT; and it showed that my reds (blood cells) and my platelets had collapsed again, sort of to the level at which they were in the diagnostic period.

And, of course, the first thought in my mind, since this was presenting very similarly to the leukemia symptoms was, I've got a recurrence here. But they did a virus scan

which showed that I had rhinovirus and RSV (respiratory syncytial virus), and then shortly after that I went into see a pulmonologist who determined that, in fact, I had quite severe pneumonia. I was at about 50% lung function at that point in time.

When I had my initial diagnostics, it was a case of going from running 7-minute miles to running 9 or 9-1/2 minute miles. This was a case where I could not walk up a flight of stairs to get to my bedroom in my house without gasping. I could not sleep through the night without waking up and hacking and having to sit up so that the phlegm would sort of migrate down in my lungs, that I would have sufficient space to breathe.

This culminated in getting a bronchoscopy, which almost led to a subsequent hospitalization at that point. But I was put on prednisone, which chased this out of my system. It came with a whole battery of different side effects, but it began the process of driving the pneumonia out.

But it took essentially one full year to get back to 100% lung function after the shingles shot, and it took nine months after the initial onset of treatment with the prednisone.

At that point, we revisited the re-vaccination because, both my treatment team and myself, felt strongly that if there is a way that I could be safely re-vaccinated, that being a vaccinated person in the world was a better thing than not. And I think that there was a general hope or belief that the problem had been a one-off, and some much more cautious protocols were put into place so that the treatments would be spaced out further apart and be done one at a time rather than in multiple increments.

I began with the third shot in the COVID protocol, which was approved for immunocompromised patients. And I immediately had a problem very similar to the one that I had had with the shingles shot one-year earlier of a fairly high fever and breathlessness and fatigue. I had another pulmonary function test, and the pulmonary function test showed not quite as bad lung function as it had a year earlier; but it

showed vastly below normal lung function, which led to yet another lung scan, which showed that I had pneumonia yet again.

So, I was back on the prednisone, and again I'm making good progress. I've regained about half of the lung function that I've lost a couple of months after treatment on this, and I'm hoping it won't take a year to get fully back to where I was on it.

But it's been very difficult going through that because as these things repeat themselves, it gets harder to treat them as one-offs. I have concerns from Dr. Shizuru's colleague that I may have some scarring in my lungs as a result of this. And perhaps, most worrisome for me is the fact that having had this happen twice, I think there's a real question about whether I will be able to get successfully and fully re-vaccinated in the future, which presents its own set of problems. It has been an unexpected and unwelcome detour on the road to recovery in all of this. And an unusual one, I believe, because in talking to Dr. Shizuru's colleague, she said that while it's not totally unusual, that she's experienced somebody having a problem once with this, that this is a very rare instance where she's experienced somebody having it a second time.

So, I think that as I eventually get past the pneumonia and get off of the drugs which are being used to treat it, that there will be further review to try and figure out why this has been happening and what, if anything, we can do to prevent it from happening in the future and what the risks of further vaccination are vis-à-vis the risks of being unvaccinated as I go forward on this.

Elissa: Dr. Shizuru, is it common for patients to have challenges with re-vaccination? What often happens in that case?

Dr. Shizuru: Well, to go back in terms of why patients would have issues with vaccination, when you get a transplant from a donor, I said we're transferring in the blood system; but we're also transferring in the immune system. And in that donor,

that immune system is set up to tell what is the difference between what belongs in that donor's body and what it needs to reject.

And so, when you transfer a blood immune system into a recipient, it takes time for that system to get to know and set up and respond appropriately to challenges. So, we have to watch our patients really carefully for many months to years to see that they don't have an overreaction, like an autoimmune reaction.

And so, that's what it sounds like when Peter described what he had with the shingles shot. He may have had sort of the overzealous response on the part of the donor's immune system. And then on top of that, with his travels and picking up two viruses, probably had an overzealous response from the immune system. And so that led to the findings and the outcome in his lungs. So, it affected his lungs in terms of having inflammation in his lungs and that's why he was given prednisone.

Now going back to re-vaccinations, I think that we actually are vaccinating people more than we used to. And the COVID vaccine is a different kind of a vaccine. I think that what we're learning more and more in the allogeneic setting is that when we do give the vaccination that there is the possibility that we're going to reactivate chronic graft-versus-host disease.

And when Peter says pneumonia, it's actually in the form of like this overzealous inflammation in the lung which requires the immune suppression. As time goes on, especially with the numbers of vaccinations that we're looking at, I think we may, in our transplant patients, see a more recrudescence of these kinds of issues that affect not just the lungs but other tissues. It's definitely an aspect that the transplanters are looking at very carefully; and we'd like to be able to sort out what are going to be the recommendations in terms of re-vaccination to Peter's point.

Margie: Doctor, let's talk about emerging treatments. Is there anything that you're excited about? Anything that's on the horizon?

Dr. Shizuru: Yeah. We talked about the development of these monoclonal-based therapies, the bispecifics, maybe even more multivalent trispecific antibodies that are being developed, and the CAR T cells. Those are the initial generation. And we can foresee that there's going to be more and more development of stronger agents.

Also, in terms of being able to probe the genetics of ALL more, that's also evolving in the basic science literature, understanding the mutational drivers in ALL and then being able to correlate it with what are the outcomes and what kind of treatment should then we stratify patients to?

In my own laboratory, we're working on a monoclonal antibody-based approach. What Mr. Feinberg described the side effects of the condition that he had with busulfan which caused the mucositis and really just fatigue and it also has other side effects, but particularly it's problematic along the GI tract.

And so, what we are developing is also a monoclonal antibody that can potentially replace busulfan, because busulfan wipes out the blood-forming stem cells. And so, our antibody, which targets a molecule called CD117 also targets the primitive stem cells, and the progenitors, and also potentially the leukemic-inducing cells; and so that's what we have under development. We've tested it in clinical trials of nonmalignant disease and malignant disease as well.

Elissa: So, is that something that could help with transplant?

Dr. Shizuru: Absolutely. It's meant to be able to replace the busulfan that Mr. Feinberg went through, the chemotherapy that we use to wipe out the blood system. It's a first generation, but that's why we look to agents like the blinatumomab. Can we link the antibody to another receptor and bring the cells in and more effectively and, I guess, naturally kill the cells without needing chemotherapy.

Margie: I'm sure that our listeners are very appreciative of your hard work and what you're doing with your team. This is wonderful news.

Dr. Shizuru: Yeah. And I do want to thank Mr. Feinberg. He has really taught me a lot about the patient experience. I've been doing this for 25 years, but he is very, very clear and articulate, taking me through his journey. I'm really very appreciative of and honored that I'm his doctor.

Peter: I feel the same way back. I think 90% of the time, my doctors love me for the fact that I do a lot of research on what I've got and I ask a lot of questions. And 10% of the time it drives them up a wall, and I appreciate Dr. Shizuru for hanging with me on that 10%.

Elissa: And this is the very reason why we do podcasts, to educate patients so they can go back to their doctor with this information. So, we really appreciate you sharing all of this, both of you.

So, to finish out our podcast, Peter, on our patient podcast homepage, we have a quote that says, "After diagnosis comes hope." Based on your cancer journey, what word would you choose to complete that sentence? After diagnosis comes?

Peter: Wow, that's a tough question. Certainly hope. One of the things that Dr. Shizuru shared with me relatively recently is that she feels that I will find my best self around the fourth-year anniversary of the transplant.

I remain hopeful that I will have a full and almost equally healthy life to what I would have had if this did not occur. In the shorter term, there are absolutely a lot of bumps that I'm going through; and it doesn't quite fit into your sentence. But I would say it's complicated.

Elissa: Yeah.

Peter: I'm so grateful for the medical care that I've gotten. I'm so grateful for my sister for being my donor, for my friends who've stood by me and my wife as I've gone through this process. But it's been hard, and I had thought that while this would not quite be like fixing a broken arm, that there would be more of a straight upward-facing

channel that has sometimes been the case; and sometimes I get the sense from my friends of, "We thought you were done with this when you got out of the hospital. What's wrong with you here?"

So, it is a complicated process; and one of the aspects of this process is, one of Dr. Shizuru's colleagues at Stanford, who you have an appointment with about a month before you get the bone marrow transplant, is a social worker who's first question is, "Why do you want to put yourself through this?" Obviously, when I went through it, there didn't really seem to be much of a choice other than dying; and anything is a lot better than dying. I really feel like I have most of my life back, and I hope I can continue to get even more of it back; but it's a hard process.

And people really do need to be prepared for a lot of ups and downs in it. It's a long, tough recouperation physically and psychologically.

Elissa: Yeah, absolutely. As they say, healing is not always linear. It seems to be definitely more of a squiggly line.

Now regarding hope, a question to you, Dr. Shizuru. With current treatments and those on the horizon, what would you say to patients and their families to give them hope after a diagnosis of ALL?

Dr. Shizuru: Well, I've been seeing how in the last 15 years, there's been the emergence of these newer agents that can give you targeted depletion and eradication of disease.

I think that as I see where we are from the academic side and the biotech side, there's such a rapid accrual of knowledge and the desire to really utilize that knowledge to benefit patients that there's no question that the breakthroughs will continue to come and that we're kind of at the beginning in some ways, in that there will be newer treatments that are going to emerge. And it's accelerated now. It's not like 20 years ago.

I also want to say to my patients and patients out there is, I think we doctors know that you are some of the most amazing and bravest people and it really is an honor to serve and work with you and be on your team. So that's what I want to say from the bottom of my heart.

Elissa: That's beautiful.

Peter: I really appreciate that. And I want to say, especially to you, Elissa and Margie, that as I have started healing that really one of the great privileges in my life has been getting involved as a volunteer with LLS, in particular doing [Patti Robinson Kauffman] First Connection®, which was so helpful to me when I got my diagnosis to talk to someone about the process of what this is like and getting through it and having them ask me a lot of the exact same kinds of questions that you've asked me on this podcast today.

Elissa: Absolutely. Well, we will have information on that in the show notes if people want to get involved with volunteering like you, so thank you.

And thank you both so much for joining us today. We really appreciate this all-encompassing conversation on ALL and all the current and new treatments; and there is so, so much hope for adult ALL. So, we really appreciate you both.

Peter: Thank you very much. I really appreciate the chance to speak about my experiences.

Dr. Shizuru: Thank you so much.

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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