LEUKEMIA & LYMPHOMA SOCIETY®

THE BLOODLINE WITH LLS

A PODCAST FOR PATIENTS AND CAREGIVERS

Episode: 'How CAR T-cell Therapy Gives Hope to Cancer Patients'

Description:

Join us as we speak to Dr. Caron Jacobson, an Assistant Professor of Medicine at Harvard Medical School and a lymphoma physician and researcher at the Dana-Farber Cancer Institute. In this episode, Dr. Jacobson shares about the use and benefits of CAR T-cell therapy in B-cell cancers, such as diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL) and chronic lymphocytic leukemia (CLL). You will hear about how CAR T-cell therapy works, why it is used for B-cell cancers and the benefits of joining a clinical trial for this type of treatment.

Transcript:

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

Edith: I'm Edith.

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

Elissa: Today we will be speaking to Dr. Caron Jacobson. Dr. Jacobson is an Assistant Professor of Medicine at Harvard Medical School and a lymphoma physician and researcher at the Dana Farber Cancer Institute.

Her research interests are in the use of cellular therapies, including CAR T-cell therapies for the treatment of lymphomas. She also serves as the Medical Director of the Immune Effector Cell Therapy Program at Dana Farber, which oversees their standard of care cell therapy program as well as their research program of a variety of types of engineered cell therapies for the treatment of both hematologic and solid tumor malignancies.

Welcome Dr. Jacobson.

Caron A. Jacobson, MD, MMSc: Oh hello, thanks for having me. Excited to be here.

Elissa: So, let's get to know you a little bit first. What brought you to the field of medicine?

Dr. Jacobson: I think for as long as I can remember, I've loved science. Been really drawn to the question of, you know, how things came to be, how our bodies work, and things like that. I think when I was growing up, I thought I'd be a veterinarian because I loved animals so much, but then I realized animals can't tell you when they're sick or when they're hurt, and, felt that would make it very challenging to be a vet.

Elissa: Yeah, that makes a difference.

Dr. Jacobson: Yeah. And so, I went to college knowing that I was going to focus on biology and get a Bachelor of Science in biology and really kind of narrow down my focus onto the studies of cellular biology and genetics. And I thought maybe I would get a PhD, maybe I would get an MD/PhD, and after spending about two years in a laboratory, I realized you could get so far removed from the actual effect that your work could have by being in a laboratory that I decided it was too far removed from human medicine and then I decided to go to medical school.

But it's that sort of love of how cells work and how cells are programmed genetically that really brought me to oncology because it's really the field of medicine that I think is informed so much by what is happening on a very cellular level.

And on a personal side, I think being part of a team that helps people when they're vulnerable and they need help that gets to celebrate in people's successes in a very intimate way and also holds people hands through the hardest times has been incredibly rewarding to me. Every day is a different day. Every day has a new set of

challenges and a new set of things to celebrate, and it makes it much easier to get out of bed every morning and do what I do. I really love my job.

Elissa: Oh, that's great. And now you also interned under our own Chief Medical Officer, Dr. Gwen Nichols, when you were at Columbia, correct?

Dr. Jacobson: Dr. Nichols is really one of the first role models I had for sort of how to be a doctor and how to be the best kind of doctor possible and then also how to contribute to science. I've looked up to Dr. Nichols ever since I met her when I was in medical school at Columbia also, so, yeah, she's a phenomenal inspiration.

Elissa: When we were looking into doing a CAR T podcast, she wrote us back and said, "Caron Jacobson, she interned under me." And so we we're happy to have you today.

Dr. Jacobson: Oh, that was very kind of her. If she asked me to do anything, I'd say yes.

Elissa: Wonderful. So, one of your research interests is CAR T therapy. Could you tell us what that is?

Dr. Jacobson: Yeah. So it's a new way to think about treating cancer. So we've learned a lot about immunotherapies to treat cancer. They're drugs that we can give to people to sort of harness the immune system or repurpose it so that it could, hopefully, fight cancer cells, but they have limitations. And some of the limitations are that the immune system, even when it's turned on, doesn't recognize cancer cells as foreign, as something that needs to be gotten rid of, and then also that even to turn on the immune system that's there, sometimes the immune system is outnumbered, and the cancer can continue to progress. The tumor and the other cells within the tumor sometimes have very inhibitory effects against the immune system, and so even when you try to take those brakes off, you just cannot activate the immune system sufficiently.

So, the idea behind CAR T-cell therapy is that it can overcome those three challenges to immunotherapy. For most of the CAR T cells that we're going to talk about today, we take the T-cells, or immune cells, from the patient themselves through a process called leukapheresis, which is generally a one-day process. We then send the cells to a laboratory where they get genetically modified, so they get some new DNA put in them that expresses a receptor on the surface of the cell called a chimeric antigen receptor, or CAR. And that chimeric antigen receptor has two parts. One part is outside the cells which recognizes a specific protein on the surface of the tumor cell, so it's the thing that targets the tumor; and then on the inside of the cell, there are a couple of on switches for the T-cell, so they serve to help activate the T-cell to kill the cell that it binds to using the receptor that's outside of the cell.

And so that's really what CAR T-cell therapy is, when the cells are manufactured and expanded outside the body to then come back to the cancer center where we give them back to the patient after a couple of days of gentle chemotherapy, which is really meant to make the patient a better host for the T cells once we give them back. And then we give the T cells back, and we wait for them to do what they're supposed to do, which is, circulate around, find the cancer cells, bind to them, and then, hopefully, kill the cancer cell once it binds to them. We've had tremendous success in a number of heme malignancies that I'm sure we're going to talk about today.

Elissa: Oh yes, definitely.

Edith: But first, what got you interested in studying CAR T?

Dr. Jacobson: Based on some of the work that I did with Dr. Nichols back in residency in medical school, my interests were largely in lymphomas. I really have always been fascinated by immunology in general; the idea that our immune system can evolve after we're born to be able to combat all the different infections that we experience in life and that it can do that, involving a process that involves changing genetic material without, causing dramatic danger or injury to the person, except when

it can cause a lymphoma. And so that sort of intersection between immunology and cancer really arrives at lymphoma.

And so, I did my research fellowship in a transplant immunology lab always knowing that I was going to come out of it in order to treat lymphoma. But I decided to focus on the role of the B cell, one of the types of our immune cells, in causing graft-versus-host disease after allogeneic stem cell transplant or a donor stem cell transplant. And I did that so that I could learn as much about B cell biology as I possibly could so that I could then apply it to different therapies for lymphoma where some of that biology gets co-opted to lead to cancer.

And it was sort of that training in immunology combined with my clinical interest in lymphoma that made me an obvious choice to run some of the CAR T cell studies when CAR T cells became a thing that we were testing in lymphoma. So, I can't say that I was sort of on the CAR T cell bandwagon at the very inception of some of these really pivotal, early phase clinical trials that happened at places like the University of Pennsylvania and at the NCI (National Cancer Institute). But when those studies led to the pivotal trials that led to some of the FDA (U.S. Food and Drug Administration) approvals that we have seen recently, that when those trials came to Dana-Farber, I raised my hand very, very high so I could be part of these studies because it really blended all of my interests in medicine. And I have to say I feel like I won the lottery.

Elissa: Aw, that's great. And that's so exciting to be able to take part in new clinical trials and new studies and just see where this could go.

Dr. Jacobson: Oh absolutely! A lot of things that we do in medicine are really incremental, but CAR T-cell therapy from the beginning has been revolutionary. And so, to see things change as quickly as they have and as dramatically as they have with the institution of one new therapy, I have to pinch myself sometimes. I can't believe that I'm getting to see this on the front lines.

Elissa: In today's episode, we would like to focus on the use of CAR T for CLL, chronic lymphocytic leukemia, diffuse large B-cell lymphoma (DLBCL), and mantle cell lymphoma (MCL). Could you start by telling us about these types of cancers, what they are?

Dr. Jacobson: Yes. They're all cancers of B lymphocytes. And as I mentioned before, that was really what I studied in the laboratory during my research fellowship. But B cells are one of our two main types of lymphocytes. The other main type are T cells. And so, these are all cancers of B cells, and they differ in terms of their biology and their natural history.

So chronic lymphocytic leukemia is the most common type of B cell malignancy that we diagnose in the United States. It is often a very slow-growing disease with a very, very long natural history, although, of course, there are some subsets, and we can identify them by certain genetic markers and molecular markers, that tend to be more resistant to therapy and maybe progress more quickly. And outside of allogenic stem cell transplant, it's typically an incurable malignancy, meaning our therapies will control it for some period of time, but given enough time, we know the CLL will progress and need to be re-treated in some future timepoint.

Now many people will CLL, may not need treatment for their entire life and others may only need one treatment in their entire life, but once we start getting through two and three and four lines of therapy, even though we've had tremendous advances in our therapies for CLL, we do start to think those patients are an unmet need. They need another therapy that can really transform the natural history of their disease.

This is a disease that generally presents with circulating cancerous B lymphocytes in the blood, so the white blood cell count could be high. It's often involving the bone marrow and the spleen, and it can involve lymph nodes as well. As I said, for many patients with CLL, the therapies are really quite effective, and they can live a long

natural history; but there are a subset of patients that cycle through these therapies and have high risk cytogenetics that really do need additional options.

The diffuse large B-cell lymphoma is the most common non-Hodgkin lymphoma that we diagnose in the United States, whereas CLL is the most common B-cell malignancy we diagnose. It is different than CLL in that it is a fast-growing cancer. So, it's a cancer of B lymphocytes that usually presents because the cancer is making somebody feel sick, and patients do need treatment right away.

We treat this generally with R-CHOP or an R-CHOP-like chemotherapy with the intent of hoping to cure the lymphoma making it go away for good. If it were to come back or not respond, this is an instance where a different chemotherapy regimen followed by a stem cell transplant from the patient's own stem cells can also be curative. But when that doesn't work, we really were without curative options, and this was a disease that was eventually going to prove to be life-limiting for patients.

Elissa: Right.

Dr. Jacobson: And so that, that's really the unmet need for patients with diffuse large B-cell lymphoma. And we'll talk about what we've done to meet that need.

And then for mantle cell lymphoma, like CLL, it's an incurable malignancy of B cells. It's also a non-Hodgkin lymphoma. It has a shorter general life expectancy than CLL does for patients, and we typically treat it when it needs to be treated with chemo/immunotherapy with or without a consolidation autologous stem cell transplant. And when it relapses, we typically treat that with one of the new class of oral drugs called BTK inhibitors for which ibrutinib and acalabrutinib and zanubrutinib are good examples. But when it progresses after those therapies, we worry about those patients because they can progress very, very quickly. And that really represents the unmet need in mantle cell lymphoma.

Elissa: Now why are these patients with these types of blood cancer good candidates for CAR T? Are there specific factors that you're looking for that would make a patient a good candidate?

Dr. Jacobson: Yeah. So, there are two questions I think there in one. So one is, are there cancers that are good candidates for CAR T, and then are their patients that are good candidates? So if you think about what I told you about how CAR Ts are developed, they're developed where the receptor is targeting a specific protein on a tumor cell. And so in order for the CAR T cell to be effective, that protein really has to be on all or most of the tumor cells, and it has to be necessary for that tumor cell to survive because if the tumor cell could get rid of it and still live, that would increase selective pressure to lose that target and then the CAR T cells wouldn't be effective. You want the cell to have a target on its surface; it's necessary for the cell to survive. But it also can't be present on normal healthy tissues because, remember, these CAR T cells are going to launch an immune attack on any tissue that has that target on it. And so, if it's present, let's say, on the GI tract, then you're going to get an immune response against the GI tract which would lead to intolerable toxicity.

So, for B cells the target that emerged was CD19, which is, present on all or most of the malignant B cells of these kind of cancers that we're talking about today, and it is necessary for the cell to survive so it's not easily lost. And the only healthy cellular counterpart that it's present on is the normal B cell. And we know patients can survive without normal B cells because there are some people who are actually born with genetic syndromes that lead to B-cell aplasia or absence of B cells-

Elissa: Oh.

Dr. Jacobson: -and we can support their immune system by giving them intravenous immunoglobulin, which is the proteins that the B cells make to help protect us from infection, to protect them from infection. And so that was what really made identifying CD19 made all of these cancers that are CD19 positive good targets for CAR T cells.

But then in addition, and I'm sure we'll talk about it in a little bit, but these CAR T cells have some side effects, and they have different side effects than our traditional cancer treatments do. Specifically, they cause something called cytokine release syndrome (CRS), which is an inflammatory syndrome caused by the activation of these T cells. And it can be quite extreme. It can be as sort of simple as a flu-like illness but as extreme as having patients go into shock or extreme respiratory distress. And then they also cause neurologic toxicity, which, thankfully, is largely reversible and meaning that patients have it for a limited period of time, but it can be quite profound and actually quite traumatic for family members to watch. The patients can get really confused and behave unlike themselves.

And so, because of these toxicities, we really want to offer these CAR T cells to patients who really don't have other good treatment options. So, I think identifying patients that are at these unmet needs that I talked about before where treatment options are more limited is exactly the group of patients that you might want to test this in from the get-go.

Elissa: So very similar to kind of what we're looking at with a transplant that there are these possibilities of complications and side effects to where maybe it might want to be, after we have tried other things?

Dr. Jacobson: Yeah. I think that that's true. I think one thing that we're learning about CAR T cells is that they may work better the earlier we are in the patient's treatment, because, if you remember, these T-cells are being collected from the patient themselves and so not only are these cancer patients where their cancer may affect the health of their immune system, but every therapy they get can affect the health of their immune system. And so, we are learning that these CAR T cells, while very effective even in later lines of therapy, may actually be better in someone who's less heavily treated. And so, if that's the case, we may want to implement them earlier.

But I think it's important to sort of understand how beneficial they are to patients and to assess the risk-benefit ratio as you get more information. I am optimistic that in certain circumstances, we may be able to move these into earlier lines of therapy in a safe way just because they are so effective and we're getting so much better at managing some of these toxicities.

Lizette: And some of the CAR T therapies are approved therapies for certain diagnoses and there are still a lot of CAR T-cell therapy clinical trials going on for other diagnoses. Can you talk about which ones are approved at this point?

Dr. Jacobson: Yeah. So, we have three FDA approved CAR T cells that target CD19 in diffuse large B-cell lymphoma. It's axicabtagene ciloleucel, or Axi-cel; it's tisagenlecleucel, or Tisa-cel; and it's lisocabtagene maraleucel, or liso-cel; and they're all approved for diffuse large B-cell lymphoma that has been treated with two prior lines of systemic therapy, meaning any therapy that treated the whole body.

And so, essentially, these are patients that would've gone through their first line of therapy, relapsed, tried a second line of therapy, and either didn't respond to that therapy or if they did respond and have an autologous stem cell transplant, then relapsed after the autologous stem cell transplant.

For mantle cell lymphoma, we have one FDA approved therapy. It's called brexucabtagene autoleucel, or brexu-cel. It is actually very closely related to Axi-cel which is approved for diffuse large B-cell lymphoma except there is one extra step in the cellular manufacturing process so that the CAR that comes back to the patient actually looks exactly the same as Axi-cel but because each therapy is defined by its manufacturing process, it actually has a new name. And that is FDA approved from any relapsed-refractory mantle cell lymphoma without any real prescription for the number of prior lines of therapy or what those lines of therapy must've been.

Axi-cel is also FDA approved for follicular lymphoma, that's relapsed after two prior lines of therapy. And Tisa-cel, or tisagenlecleucel, is also approved for pediatric and

young adult B acute lymphoblastic leukemia (ALL) that has relapsed after any prior line of therapy.

We have no FDA approved therapies for CLL at the present time, but there are ongoing clinical trials exploring CD19-directed CARs in CLL as well as novel targets, so CARs that are directed against different tumor proteins to see if we can land on the best therapy for patients with CLL.

Lizette: I know at the beginning when we started talking about CAR T-cell therapy years ago, doctors were talking about CAR T-cell therapy sometimes as a bridge to getting a patient to be able to get a transplant. Has that changed because now I hear a lot of doctors talking about CAR T-cell therapy as the possible cure?

Dr. Jacobson: Yeah. I think that speaks to the fact that we've been pleasantly surprised by how powerful this therapy is. So, let's take diffuse large B-cell, for example. So, each of the three different therapies that I mentioned, in a single infusion to a patient with refractory diffuse large B-cell lymphoma, we can see anywhere from 50 to 80% of patients respond, and we can see anywhere from about 40 to 55% of patients have a complete response, meaning their lymphoma goes into remission. And for some of these studies, we have four-year follow-up, and at four years, it looks like 40% of these patients have not relapsed. They're alive and free of relapse, and so it looks like we probably are curing about 40% of these patients. So, in this disease in particular, I would not think that CAR T is a bridge to anything. I think it's a definitive therapy for up to 40% of patients and, remember, these are patients that didn't have a curative option prior to CAR T-cells.

I had mentioned that we don't have a cure for mantle cell lymphoma outside of an allogeneic stem cell transplant; and most therapies in this line of therapy would be expected to lead to a partial response in a subset of patients and a very short partial response at best.

In the pivotal trial of Brexu-cel for mantle cell lymphoma, Brexu-cel's also known as Tecartus®, we saw that almost 70% of patients had a complete response to the single infusion of Tecartus or Brexu-cel. And this study has 18 months median follow-up, so half the patients were followed for more than 18 months; and half were followed for less than 18 months. But at that timepoint, at 18 months, it looks like 60% of patients are still in response, which is very encouraging. There may be a subset of patients with mantle cell lymphoma that we can cure and that we may actually be changing the natural history of this disease.

And I think the same is sort of hoped for and expected in CLL. It's just trying to find the right target and the right combination of cells to do that.

Lizette: We've been so lucky to be able to speak to so many CAR T-cell therapy patients, who were not doing as well on prior treatments. And they had CAR T-cell therapy, went through it. Like you said, there are some effects afterwards, but they are so happy, and they are thriving. They are living their lives and are so thankful for CAR T-cell therapy, and it's really great to talk to them. Right, Elissa?

Elissa: Oh, yes. It's so amazing just to hear all of these advances that have really just exploded in these past few years and to see patients surviving longer and just doing really well.

Let's talk about some future possibilities. In January 2021 interview with *Cure Today* magazine, your colleague at Dana Farber, Dr. Matthew Davids, discussed the future of CAR T for younger patients with CLL. He said that, particularly for younger patients who had relapsed with prior treatments, there might be possibilities of using CAR T as an alternative to an allogeneic stem cell transplant. While this isn't an approved use yet by the FDA, could you tell us more about it?

Dr. Jacobson: Yeah, I mean I think when we meet a young patient with CLL, even if they have good risk disease, we do worry about them just because we want them to live their natural life; and that's going to be decades, right? I hope that over the

course of those decades, we have lots of new therapies that will benefit that patient in particular. There's always a possibility that that patient will cycle through the available therapies; and before CAR T, I think we all thought that that was, that patient had a high likelihood of potentially needing a donor stem cell transplant in that setting as we discussed. It was sort of the last resort, the thing that you do when you don't have a plan B after the line of therapy that the patient's on because that is a curative therapy for CLL, although it does carry some risks of mortality as well as morbidity, which I don't think should be overlooked.

Just as with mantle cell lymphoma, we're seeing 60% of patients still in response at 18 months; and I hope that's going to be a similar number that we see at 24 months and 36 months. There's no reason to think we can't achieve the same thing in CLL; the studies are just not as mature. But if we can achieve the same thing in CLL, if we can use this cellular immunotherapy to get rid of every last CLL cell in the body, then there won't be a need for an allogeneic stem cell transplant, that this may be the definitive therapy for some of these younger patients, which would be phenomenal.

Elissa: When do you see that potentially, actually happening? As we continue to collect data, how long does that usually take until you realize that, yes, this could actually work and then go for FDA approval?

Dr. Jacobson: So, I think with CLL, it's interesting, right, because the very first case report of CAR T cells in *The New England Journal of Medicine* came out in 2010; and it was a CLL patient that had relapsed after every line of therapy and got the CAR T cell that was to become tisagenlecleucel or Kymriah®. And this patient did phenomenally well. We're 11 years later and this patient, as far as I understand, is still in remission.

And so, people thought CLL was going to be the poster child for CAR T-cell therapy. But then we started to treat more and more patients on these trials with CLL, and we realized that it benefitted about a quarter of the patients; and 75% of the patients did

not benefit, so not the same numbers that I told you about for mantle cell lymphoma or diffuse large B-cell lymphoma.

And the group at the University of Pennsylvania did some work to try to understand this, and they realized that the CAR T cells that were manufactured for patients that responded favorably led to response in animal models of CAR T cells whereas the CAR T cells that were manufactured for patients that didn't respond, those CAR T cells didn't work in the same animal models. And so, it told us that it had something to do with the T cells themselves that were collected from the patient and then used for manufacturing.

We know that CLL is a disease that interacts with the immune system in unique and unpredictable ways. And so, for some patients, that interaction led to very productive T cells; and for others it led to less productive T cells. So, a lot of the work right now is trying to figure out how we can optimize the T cell health in a CLL patient before we collect their T cells so that we can improve those numbers and maybe even flip them, right, because 75% complete responses and insufficient responses in 25% of patients.

And we're getting there. The liso-cel product that was FDA approved for diffuse large B-cell lymphoma is in clinical trials in CLL. It's called the TRANSCEND CLL study. And we saw some results at the ASH (American Society of Hematology) meeting last December that showed that we are achieving responses in 70 to 80% of patients and complete responses in about half of them. And when we follow people out for 12 months, we're seeing half of them maintain their response. So, I think we're getting closer to a potential FDA approval and really sort of inverting those numbers, like I said, so that we can really benefit these patients.

But in addition, we're starting to see CAR T cells that are developed against different tumor targets in CLL to see if we can improve the outcomes. And so those are trials that are sort of in their infancy.

And then we're also starting to look at allogeneic CAR T cells where we actually collect the T cells from a healthy donor that doesn't have a malignancy and hasn't had prior cancer therapies. Those T cells are manipulated in a way that doesn't allow them to cause graft-versus-host disease. And the benefit of this is that we can collect multiple products from one patient and these products are available off the shelf; and they are potentially healthier T cells, right, because they're coming from a healthy donor.

So far, the problem with these strategies has been that the host, the patient, launches an immune attack on the donor T cells before the donor T cells can have an anti-cancer effect. But all the companies that are exploring this option are now tweaking that gentle chemotherapy that we give to patients before we give them back their CAR T cells so that the host immune system is suppressed sufficiently to allow the donor T-cells to do their job. And so hopefully clear the malignancy. That's another avenue where we may actually see another type of therapy in the cellular therapy space that could benefit patients with CLL and can overcome some of the reasons that it's been a challenge so far.

Edith: As Elissa mentioned in your introduction, you are the Medical Director for the Immune Effector Cell Therapy Program. What is Immune Effector Cell Therapy?

Dr. Jacobson: So, it's really any therapy where we use immune effector cells, so it's immune cells that can actually have a cell killing effect to treat a disease. And so, the poster child for this is CAR T-cell therapy, but there are other examples of immune effector cells.

So, we do trials using engineered T cell receptor T cells where instead of having a chimeric antigen receptor on the cell surface, it's an engineered T cell receptor against a tumor target. We also do trials involving another type of immune cell called an NK cell, these NK cells can be unmanipulated or they can also express like CAR on their surface.

We do trials looking at tumor infiltrating lymphocytes, which are recovered from a tumor biopsy from a patient and then grown in culture and activated and then given back to the patient with the hope that the T cells were there to begin with because they can recognize the tumor cells. And by giving them back in greater number and in an activated state, they can actually kill tumor cells.

So, there are a whole host of different types of immune effector cell therapy, and each one of them has its pros and its cons; and some might be better suited for treating blood cancers, and some may be better suited for treating solid tumors. But this field is growing exponentially, and so our program now, not only does it support the four FDA-approved products in lymphoma and leukemia, as well as the newly FDA-approved product in multiple myeloma, which we don't have time to talk about today, we also support the entire clinical research enterprise exploring new and exciting products across the cancer center.

So, we continue to treat blood cancers, but we're extending our focus into solid tumors as well. And so, we have clinical trials now in every single disease center at Dana Farber, and that's a testament to how exciting this therapy is and how much hope it can bring across the board in cancer care.

Elissa: That is just really exciting. Could you tell us why a patient should consider participating in one of the trials that you have going on in your program?

Dr. Jacobson: Yeah, of course. I mean I think whenever anyone agrees to participate on a trial, you are going out on a limb to some extent because the reason it's in clinical investigation is because we don't really know how beneficial it will be. Obviously, we have evidence from the laboratory and good rationale for trying something, but so many times people are trying things because they have limited other options.

But in this case, the cell therapies have a track record where they have been incredibly beneficial. I think that every patient's going to consider the pros and cons of different

therapies and their side effects and their potential for benefit differently. But some people with CLL or with mantle cell lymphoma or with follicular lymphoma have been on therapy for so long, right, continuous therapy where they haven't had a break.

The idea of a single infusion of any one of these therapies and then followed by a break, one where you just have to go see your doctor for a checkup, and you don't have to come for an infusion or for toxicity management or things like that is really a relief to a number of patients. And so, I think this very time-limited therapy with a single infusion is appealing, that this is a type of therapy that I would encourage people to explore.

Obviously, if you fall within the eligibility criteria for one of these trials and it's an established therapy but just looking at a different line of therapy, so either earlier in your disease course or in combination with another therapy, the data really speaks for itself. And then, obviously, what we hope is that we create options for people who didn't have options before. And so, if options are running out, that would absolutely be the best reason, I think, to participate in one of these trials.

Elissa: Right, definitely. So even though, with CAR T becoming a lot more popular and a lot more known in the cancer world, do you still find some hesitation when it comes to getting onto a trial?

Dr. Jacobson: So, I think the biggest hesitation we've seen is in referral patterns, actually. So, to be honest, I think patients are very educated about this and tend to come to us wanting this. Some people come to us wanting it before it's indicated because they can be so educated about it. But it's the physicians in the community that tend to be reluctant to refer, either because they're not aware of all the different clinical trials or the different therapies that are offered or because of maybe some myths about the toxicity and who the right patients are.

I think it's important to know that every single center that offers CAR T-cell therapy will have a different set of criteria by which they sort of assess whether a patient is a

good candidate for CAR T cells. I can tell you at Dana Farber we were very strict in terms of heart function and kidney function and other medical problems when we first started, and we've become very liberal since then because we've realized that we can adequately manage these toxicities and get people through this therapy safely.

So, I think it's really important that patients and providers understand that whether a patient's a good candidate or not really should be in the assessment of the treating center. And that if a patient meets the criteria for the FDA label or for the clinical trial, they should be evaluated because I do think we're undertreating people with this really powerful therapy across the country.

Elissa: One of the things that you mentioned was that a lot of doctors don't know that there are the trials out there. And for our listeners, that is one of the great benefits of our Clinical Trial Support Center (CTSC); and the links for that will be in the show notes. But we have oncology nurses that can understand your diagnosis and the criteria that you might fit in and look for trials around the country for you. So, we're excited about the program that we have to be able to, again, get more people into the trials. So, if their own doctor might not know that this trial is going on, that our Clinical Trial Support Center can work with the patient and be able to refer them over there.

Dr. Jacobson: Yeah, I think recently you sent patients to us for our CAR T cell trial in CNS lymphoma.

Elissa: That's great.

Dr. Jacobson: Which is great. It's a mutually beneficial relationship because we always want patients to go on our trials; and then you benefit the patient by introducing them to us, so I think it's wonderful.

Edith: On our patient podcast home page, we have a quote that says, "After a diagnosis comes hope." We have just discussed the current and future use of CAR T-

cell therapy for CLL, large diffuse B-cell, and mantle cell lymphomas. What would you say to these patients and their families to give them hope for the future?

Dr. Jacobson: I think that within five years of the first patient being treated with CAR T-cell therapy, we've seen pivotal trials in a number of, of incurable diseases with limited treatment options; and now within seven to ten years, we've seen FDA approvals across the board.

And so, the pace that medicine is moving, and oncology is moving is so rapid right now, and this is just the beginning of this field, I think we're going to look back on 2021 and think that what we were doing was barbaric, even though we were curing 40 to 50% of patients. I think we are only going to improve this exponentially. We're going to be doing this much more precisely and in combinations with other drugs that are going to greatly influence the activity of these cells and the durable remission rate. I think this is the tip of the iceberg, and we've already seen basically medicine happen and fast forward; and I just can't wait for what the next five to ten years is going to bring.

Elissa: That's amazing. Well, thank you so much, Dr. Jacobson. We were so excited to hear about CAR T and all the current and future uses and the advances. It is such an exciting therapy; and to hear that it really could be that end game for a lot of cancers is just so exciting, and I really think that that will provide hope for the future. So, we really appreciate you coming on our podcast today and telling all the patients about the therapies.

Dr. Jacobson: Oh, well thank you for having me. This has really been an honor to be a part of, and I'm happy to share it as best I can whenever I can.

Elissa: Great, well thank you.

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

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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 information about our Clinical Trial Support Center at LLS.org/CTSC. All of these links will be found in the show notes or at TheBloodline.org.

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