

THE BLOODLINE WITH LLS

A PODCAST FOR PATIENTS AND CAREGIVERS

Episode: 'CAR T-cell Therapy Explained: Recovering from CAR T-cell Therapy'

Description:

On this episode, Alicia and Lizette speak with Dr. Rayne H. Rouce. Dr. Rouce is a pediatric hematologist and oncologist at Texas Children's Cancer Center where she is a member of the Leukemia and Bone Marrow Transplant programs. She works as part of The Center for Cell and Gene Therapy at Baylor College of Medicine, focused on translating targeted T-cell therapies, and has been involved in every aspect of CAR T-cell development for clinical use. On this episode, Dr. Rouce explains what types of cancers chimeric antigen receptor T-cell therapy, known as CAR T-cell therapy, currently treats, when it may be considered for treatment and why the recovery process may be different for each person. She addresses quality-of-life issues and recommends great questions about CAR T-cell therapy that a patient or caregiver should consider asking their healthcare team. Dr. Rouce shares her excitement for how she sees this therapy improving in the future and continues to work towards discovering how it can be a hopeful option for more and more patients.

Transcript:

Alicia: Welcome to The Bloodline with LLS. I am Alicia.

Lizette: And I am Lizette. Thank you so much for joining us on this episode. Today, we will be speaking with Dr. Rayne H. Rouce. Dr. Rouce is a pediatric hematologist and oncologist at Texas Children's Cancer Center, where she is a member of the Leukemia and Bone Marrow Transplant Program. Dr. Rouce has spent the past several years of her career pioneering immunotherapy research for patients with refractory leukemia and lymphoma.

Specifically, she works as part of a research program called The Center for Cell and Gene Therapy at Baylor College of Medicine focused on translating targeted T-cell therapies from the bench to bedside and has been involved in every aspect of CAR T-cell development for clinical use. She has significant clinical experience in taking care of patients who have received CAR T-cells and is passionate about ensuring patients and families understand this exciting new therapy. Thank you so much for joining us today, Dr. Rouce.

Dr. Rouce: Absolutely. I am excited to be here.

Alicia: We have done so many things with you. I feel like—we feel like we know you now, Doctor.

Dr. Rouce: We're just having a little chitchat.

Alicia: What is CAR T-cell therapy, for the listener?

Dr. Rouce: So, I'll first start by defining what a CAR T-cell actually is. So, CAR stands for Chimeric Antigen Receptor which is a whole mouthful, but all it means is that it's an artificial receptor that has been made in the laboratory to target something specific. So, to make CAR T-cells, what we actually do, is we collect normal T-cells from patients' bodies. All patients, everyone, healthy people, everyone has T-cells in their body that have a regular T-cell receptor on them that is supposed to be going around the body looking for viruses, looking for things that aren't supposed to be there, looking for cancer cells. We take these T-cells, and we take them to the laboratory, and we introduce this artificial receptor called the CAR, okay. The reason we do that is because we want the T-cells to take up these CAR's, express them on their surface so that if they come into contact with the cancer cell that expresses, kind of, the matching link to this CAR, they can target them to be killed. This process involves usually collecting the T-cells through a process known as Leukapheresis, where we collect out only T-cells from patients and return all the other parts of the blood. We take them to the laboratory. We use an inactivated virus to carry the CAR into the cell and it, therefore, changes the machinery; the whole genetic make-up of the T-cell and causes all the T-cells in the culture to express this CAR molecule. And then we feed them, and grow them with nutrients and cytokines; grow them in number; and then they are ready to be given back to the patient.

Alicia: And for those listening, we encourage you listeners to listen to our episode with Dr. Rouce in which we spoke with her about CAR T-cell therapy and how it works. And we also did a telephone web program with Dr. Rouce and Dr. Loretta Nastoupil from the University of Texas, MD Anderson Cancer Center in Houston, Texas in which they spoke about CAR T-cell therapy in children and adults with blood cancers. So, you can access that archive program by visiting www.lls.org/programs.

So, to jump into this episode, Dr. Rouce, what types of cancers can CAR T-cells treat currently?

Dr. Rouce: That's a really great question because just a few years ago, the answer would have been very different and much more limited. So, the most common cancer that has been treated with CAR T-cells are leukemias. Usually, these cell malignancies—this is like 3b ALL in children, which is the most common blood cancer, but also lymphomas that can, you know, occur in adults such as diffuse large B-cell lymphoma and also in a smaller population of children. So, leukemias and lymphomas,

but more recently, we've seen CAR T-cells targeting other types of leukemia such as AML. These CAR T-cells still remain more in the clinical research setting, but are very promising. We've also seen CAR T-cells—we have a study, for example, at our Center where we are targeting T-cells to lymphoblastic leukemia and other types of T-cell malignancies which have, previously, not been targeted using CAR T-cells. When we look at some of the other kinds of blood cancers, multiple myeloma has been targeted with CAR T-cells, Hodgkin lymphoma and anaplastic large cell lymphoma, using a CD-30 CAR; so, the sky is the limit for using CAR's to target cancer.

One thing that is really promising about leukemias and lymphomas is that they are very acceptable to CAR T-cells. They typically are in the blood, or they are in the bone marrow, or they're in the lymph nodes. So, they are not usually walled-off deep inside the core of an organ where it is hard for the CAR T-cells to get there and to penetrate. So, that is one really great thing about leukemias and lymphomas and why most of the CAR T-cells you see in clinical practice are targeting a leukemia or a lymphoma. I won't go into too much detail, but I do want to let you know that there are CAR T-cells that target brain tumors, that target breast cancer, lung cancer, pancreatic cancer, neuroblastoma, lots of different tumors. Although these are earlier in their development, there are lots of studies that have some very promising results.

Lizette: Does it matter if it's a chronic disease or if it's an aggressive disease?

Dr. Rouce: Absolutely; really good question. So, CLL, or chronic lymphocytic leukemia, as you guys know, is more of a disease of the adult and often the elderly and it also expresses CD-19. So, CAR T-cells targeting CLL have not been quite as successful; and we do think that this has something to do with the biology of the disease and the expression. So, we've seen the most benefit in acute or more aggressive leukemias and lymphomas and, while the true reason behind this is not absolutely known, we do think that that plays into it. That was a great question. We always get asked that question.

Alicia: So, as far as we know and we know that the treatment process for CAR T is, evaluation to see if the patient, is a candidate for this therapy, collection of the T-cells, engineering the T-cells, multiplication, conditioning therapy, infusion, recovery. I want to spend some time on the recovery process. What does that entail?

Dr. Rouce: Great question. So, we talked a bit, in the first podcast that we did, about some of the side effects you may expect to experience after CAR T-cells. And so, for some patients, they may have absolutely no side effects at all. They may get their pre-conditioning or lymphodepleting chemotherapy to make space for the CAR T-cells. They receive the CAR T-cell infusion, which I want to mention usually it's planned for you to receive a single infusion of CAR T-cells although there are some cases, and in some studies, where you may receive multiple. You have a waiting

period where you are waiting for these CAR T-cells to get into the body and start to take care of the cancer, kill the cancer. And then you have a disease evaluation the same way that you would if you received chemotherapy, or radiation, or any other form of cancer-targeted therapy. And after that, what typically happens is you have this, what we call, surveillance period where every so often you'll see your doctor to check your blood counts still, do a disease evaluation to see if you are still in remission, if you originally responded to the therapy. The one thing about CAR T-cells is that, depending on what the CAR T-cell is targeting, the side effect profile, and the recovery, and the long-term follow-up may be different, okay?

So, I discussed a bit about how, in the immediate post-infusion period, which most people would consider up to about 4 weeks, that's the time period where you are more likely to have a side effect such as cytokine release syndrome, which may require in-patient hospitalization; may require ICU treatment. You are more likely to experience some neurological complications that happen in a lesser degree, but can happen. But, outside of that period, most patients are managed on an out-patient basis, meaning they go home. They go see their doctor. If they travel across the country to receive CAR T-cells, they typically are allowed to go back to their home hospital and their home oncologist. And, there is not a set time point for disease evaluations. For example, if you had leukemia, initially, people may do a marrow as frequently as every month. They might phase that out to every 3 months, every 6 months basically looking for a couple of things. One thing is any evidence of the cancer coming back, obviously, but the other thing is looking for the actual CAR T-cells. In research trials, there are actual lab tests that we can do, not in the general lab like at the hospital, but in a research lab where you can actually track the CAR T-cells. For the commercial product, there are usually surrogates to track.

So, the reason I want to talk for a bit about why it's important to distinguish your recovery, or your follow-up, based on the CAR T-cell that you received is that I'll use the CD-19 CAR T-cell as an example because it's been recently commercialized, and it's the one that people ask about the most. With that CAR T-cell, it attacks the CD-19 that's present on the surface of the cancer. However, CD-19 is also present on the surface of normal B-cells, which are another type of immune cell. They are, kind of, like a cousin of the T-cells. These cells are also responsible for helping protect you against infections, especially bacterial infections. So, the CD-19 CAR, although it is very smart, it's not smart enough to distinguish CD-19 on the surface of a normal B-cell versus on the surface of a cancer cell. The problem with this is if you still have circulating CAR T-cells in your body, which is what we want, and they successfully got rid of all of the cancer that's there, they typically have successfully also gotten rid of all of your normal B-cells. So, because of this, we have to give you a medicine called intravenous immune globulin which is basically like a surrogate for B-cells and it helps you not get infections. So, this is something that people who have received CD-19

CAR T-cells usually get about once a month, okay? If you receive another type of CAR T-cell, the follow-up may be a bit different.

One thing that is absolutely imperative for everyone to understand is that because these cells have been genetically modified, even though they are your own cells, we change the genetic machinery of them. There's a very, very, very, very, very small risk and it's mainly a theoretical risk, as this does not happen in CAR T-cell trials, there's a very small risk that there could be a mutation and the cells could get confused and actually cause a new cancer, okay? Because of this, it is absolutely imperative that people who have received CAR T-cells get follow-up for at least 15 years. This is something people rarely talk about and, fortunately, in a recent review of over 1000 patients who received CAR T-cells, we see no evidence of this, but it is still something that we want to check for.

I will also say that most people, if they respond to CAR T-cell therapy within the first few months can almost go back to their normal life. So, if this is a child, as long as their blood counts are up, which CAR T-cells normally don't affect the blood count; the lymphodepleting chemotherapy we give can, but normally your blood count is back up within a couple of months, they may be able to go back to school. Adults may be able to go back to work. So, this is really an important part of the process, I think, to stress because the recovery, although it may be significant if you have a side effect like cytokine release syndrome, it is transient; and typically, you are back to your baseline within a couple of months.

Lizette: That's really big for quality of life issues, right?

Dr. Rouce: Yeah; absolutely. And I think that's one of the greatest things about CAR T-cell therapy is that when it works, patients can experience a return to a quality of life that they may not have experienced in years with any one blood type of cancer they have.

And it is also important to mention that CAR T-cell therapy is designed to be given as a single infusion. So, what this means is whereas with some other therapies you try, you may try them and they may work very well, but you move on to the next therapy after that with hopes of staying in remission. CAR T-cell is designed to be a single therapy and, afterwards, the plan is not to give you chemotherapy or not to give you radiation. The only caveat to this, and we discussed this a little bit on the first episode, is that, right now, we really can't say, "oh, CAR T-cell therapy is curative for all patients." There are some patients that will remain in remission for long periods of time, but remember this is still a pretty early therapy for patients. So, we are only about 10 years in; so, we don't have long enough data to really be able to say, the way we can with bone marrow transplant, for example, "this is a curative option." And so, some physicians, and some patients, and their caregivers, after careful discussion, may opt

to proceed to a bone marrow transplant as a potentially curative option and use the CAR T-cells as a bridge to get there.

Lizette: We get the question a lot of patients who say, “well, if I receive CAR T-cell and I have a relapse, can I receive CAR T-cell again?”

Dr. Rouse: That’s a wonderful question. The answer “perhaps” and the reason that I say “perhaps” is because it truly does depend on whether you have received the CAR T-cell on a clinical trial, whether there are actually CAR T-cells available, and, kind of, what the status is. So, for the commercial products, they are designed for you to receive a single infusion. However, there have been cases where people’s leukemia for example, has come back and, within the original manufacture, there were enough cells to give an additional infusion and they’ve received them. The same thing on clinical trials. Another specific situation is if you have, let’s say, a partial response. So, say you have lymphoma and you had it in multiple places in your body and you clear up 3 of the 4 places, then that’s a good case to give some additional CAR T-cells to try to clear up that last place. Sometimes it requires people to undergo an additional collection, a leukapheresis, to remake CAR T-cells. So, it is a loaded question, but I’m so glad you asked it because it is absolutely worth asking and I would encourage every patient, or family member who is thinking about CAR T-cells to ask their physician that.

Alicia: And also, along those same lines, what are other questions that you would recommend of a patient, or family, ask their healthcare team when it came to this treatment?

Dr. Rouse: Really good question. Good way to put me on the spot. I do think that, sometimes, patients and caregivers feel kind of bashful about asking about what the stats are. How has this worked? How many patients have you treated especially in clinical trials? I think you need to be empowered. So, no one should ever feel put on the spot or embarrassed to tell you about the results of their therapies, but keep in mind, that especially if it’s on a clinical trial basis, there may be very few patients—some of the clinical trials, their primary goal is to look at safety, so they may be able to tell you a bit more about safety and a bit less about how effective they are, but I do think it is important to ask about that. I think it is important to ask about what does this mean for my life? What are the logistics of it? Am I going to have to stay in the hospital? Am I required to stay here for a month, or for 2 months because those are important things that factor into your decision about whether you want to go on a clinical trial, for example, or whether you want to receive a therapy and where you receive it.

I think it is important to ask if you are getting CAR T-cells at an institution that’s different than yours, or with a physician, or healthcare provider that’s different than your primary healthcare provider, or your primary oncologist, or bone marrow

transplant doctor; I think it is important to ask them what the goal of the treatment is for you because, like we mentioned on the first podcast, in some cases, the goal may be you have a perfectly matched sibling donor. You've had a very aggressive leukemia or lymphoma, and you pray that this CAR T-cell therapy works to put you into remission, but considering how aggressive your disease has been in the past, we don't want to lose the opportunity to provide you with a potentially curative option, which could be a bone marrow transplant. So, I think knowing those things up front and making sure there is an open dialogue between the physician, who is in charge of you for your CAR T-cell treatment, and your home oncologist, who knows you. They know your lifestyle. Your life doesn't stop because you have cancer and go on a clinical trial or get another type of therapy. So, it is important to factor all of that in so that you could make the best, informed decision.

I think now we are very fortunate in that, with lots of research and lots more people getting involved in CAR T-cell therapy and organizations, like LLS, supporting early research in CAR T-cell therapy, the options are a lot more than they were even just a few years ago. So, we are entering an era where you actually may have multiple potential treatment options for relapse and refractor leukemias and lymphomas. And this is a wonderful thing, but it is also a stressful thing. So, I think asking those questions up front, or if your needs change 2 weeks in, 3 weeks in, 4 weeks in, all of us, regardless of whether we are researchers or regardless of whether we are primarily clinical doctors, we want to do what's best for you. We want to advance science, but our primary goal is to help patients. So, I think being forthcoming, there's no question that is stupid at all; so absolutely ask them. If it doesn't make sense, ask them. And I love your question earlier about what does the recovery look like because it is really important for life planning. Those are my go-to questions that I would force any family member of mine to ask before therapy.

Alicia: Well, Doctor, Rouce. If that is you on the spot than I would hate to see you prepared. That was incredible.

Dr. Rouce: Is there a Grammy for talking? I would win multiple times every year.

Alicia: Doctor Rouce, I think it is so great for, patients and their families to hear doctors say that because, a lot of times, like you said, they are bashful and they feel like, the doctor knows it all so I will just come to my appointment; I'll listen; and I'll leave. we very much stress the importance of shared decision-making, of open communication and making sure that people know that there are 2 experts in the room; them and the doctors.

Dr. Rouce: Absolutely; and what I will say is that the patients that I have taken care of and their families who received CAR T-cell therapy are some of the most informed people I have ever met in my life. And also noting that I may not even have heard it

all. So, they keep their ears to the street; and I think it is so important and we are well past the era of—doctors being fraternalistic and making all of the decisions. And, I will stress, that the doctor that you are seeing specifically for CAR T-cell therapy may be an expert in CAR T-cell therapy, but they are not an expert in you and your home doctor still has a role. So, never feel bashful. If you do not feel comfortable asking a question or if you are not quite sure how to phrase it, feel free to share the information of your treating oncologist because they will often ask questions that they, in their experience, of taking care of you and your family, they know that you may want to ask. So, I absolutely enjoy talking to referring physicians, answering questions. I talk to grandmas, aunties, brothers-in-law, parrots, chihuahuas, all of these.

Alicia: That is so great. And you know what, the thing about it is that I was talking to a doctor, a few years ago and they were saying, “you know, people walk into a car dealership and ask a million questions...”

Dr. Rouce: Absolutely.

Alicia: ...and then when it come to their health, they’re shy”. And so, he was saying, “you know what, we’ve got to get this—this idea out of people’s heads that they can’t ask as many questions and whatever question they want about their health.” This is their body.

Dr. Rouce: There is no question that is off limits, as far as I’m concerned.

Lizette: And I’m actually working on another communication video, strategy, and everything you just said, like both of you, was like, “oh, this is exactly what I’m doing in my other project.” I think I just wanted to bring up one thing and...

Alicia: Yeah.

Lizette: ... I don’t know if it’s a function of you treating pediatric patients, and talking to a lot of caregivers all the time...

Lizette: but it is really refreshing to see that you are comfortable in talking about all of these different things that we may not feel comfortable in asking with adult patients.

Dr. Rouce: I think it’s spot on. I know when I go into a room, regardless whether it’s a newly diagnosed patient or whether it’s a patient who has relapsed and is coming to me for CAR T-cell therapy, that my job is to ensure that everyone there is comfortable. And I also notice some people that want it to be there for discretion are not going to be there, but are certainly support givers, and caretakers, and caregivers, and love the patient whether they are one-year-old or they’re 25-years old. And so, I recognize that

a lot of the burden that comes on a parent is figuring out what best for my child, but also how to explain to all of the grandmas of the world why they made a certain decision. So, I like to take on a bit of that burden. I like to try to put myself in their position, if I could, at least in - and think about what I would want to ask. Think about the questions that I had. Think about what we thought about when we designed the therapy. Think about if it were me in that position or if it were a family member. So, I do think that that's part of it. Thankfully, in early investigational research, I think that most physician/scientists are learning that because there's a lot of unknowns about some of the therapies that we use, it is important to disclose that and then, as we gain more knowledge, I think that we kind of work it into our communication. So, I do encourage the patients because it's not always that the doctor is not willing to share the information, they may just not necessarily know or be at the forefront of their mind that information that the family might be seeking

Alicia: Such great input. Thank you for that. So, we know that there are cancers like indolent B-cell lymphoma, mantle cell lymphoma, multiple myeloma and like you said earlier, acute myeloid leukemia that are being looked at the next phase of CAR T-cell therapy clinical trials. For you, where do you see CAR T-cell therapy going in the future?

Dr. Rouse: You know, that is a great question and it's one that what I've noticed is I answer it probably about every few months to someone who asks and my answer often evolves over time.

Alicia: That's good.

Dr. Rouse: It's good. It shows how fast the field is moving. So, one of the big targets for CAR T-cell research is right now. And for CAR T-cells that we've shown to be effective in patients, how can we make them last longer and how can we make people not relapse with the same malignancy that has sneakily decided that it no longer is going to express the marker that we initially targeted. So, that is called "antigen escape" or "antigen negative relapse." So, lots of researchers, at various centers, including ours, are looking at can you target multiple markers or surface antigens on someone's cancer so that, if the killing for one specific antigen poofs out or if the cancer decides that it doesn't want to express it anymore, the CAR T-cells still have something to target as opposed to keeping the patient in remission.

The other thing is that we know that CAR T-cells need to last in the body in order for them to be effective long-term. So, lots of groups, including ours, are looking at how can we enhance the persistence and make sure that they stick around. So, really technologically savvy and fancy ways of scooping up these CAR T-cells, and not having just a walk into the showroom in the car dealership and pick the car. They have a really specialized, personalized one.

And another thing that I think is really exciting, aside from trying to look at different targets on different cancers so you could treat more people, is how can we make this therapy still have its personalized approach to be able to target a more widespread audience and make it immediately available? So, this is what we call “off-the-shelf CAR T-cell therapy”. And what this means is if the CAR T-cell, the way we typically think of it that’s targeting a certain one or two antigens or markers on the cancer cells, but it doesn’t have to be made from the patient. It’s something that can be made and engineered either to not express a different HLA than the patient, so the patient’s body does not recognize that it’s foreign and try to reject it—and there are very sophisticated mechanisms for doing that, but essentially if you relapse and you go to visit your doctor, your doctor can say, “you know what, there’s actually a CAR T-cell that may be available for you and I’m going to call this research center and see if it’s available and, no, I actually don’t need anything from you. I don’t have to set you up to have catheter in place to collect your T-cells on a pheresis machine and then wait for multiple weeks while they grow in the laboratory and hope that, during that time period, we have some other therapy that can keep your cancer under control.” So, I am really excited about these off-the-shelf CAR T-cell options that a number of groups are working on. And I think that, you know, what we’ll find from this is that we may be able to reach a wider spread population. Imagine being able to pull out the CAR T-cells from the freezer and ship them to a site and you receive CAR T-cell therapy at the hospital that is 10 miles from your home, as opposed to 10 hours from your home. That’s really exciting.

I also think as we learn more about CAR T-cells, but also the tumors that are more difficult to target, we learn about things that are in the tumor environment. We call it the “tumor microenvironments”. It’s kind of the tumor’s hood, right? The tumor’s hood is a very hostile environment. It is not welcoming to chemotherapy. It’s not welcoming to radiation. It doesn’t like our CAR T-cells. You know, it’s not a great open, you know, red carpet, welcoming, open-door environment. So, what we look at is other drugs, or ways of targeting the microenvironment, to make it a better environment for CAR T-cells to thrive so that when we put them in, they actually have the ability to do their job better. So, lots of combinatorial therapies. So, it’s really an exciting time to be a CAR T-cell researcher because there is so many exciting things and lots of great things they are doing and, again, you know, a lot of the research that we do is supported by the LLS, or otherwise, we wouldn’t be able to bring it to the clinic for patients. So, the sky is the limit and everyone will be pushing towards making a bigger, better batter, in the good sense of that, CAR T-cell.

Alicia: That is awesome; and to think of how, like you said, how far cancer has come from it being, you know, this word that was almost taboo. No one wanted to say it. You know, and for it to transform into this sci-fi process that is only, you know, evolving is so incredible and so hopeful.

Dr. Rouce: It's so true.

Alicia: So, I'm going to see if this works. On our home page, we have after a diagnosis, comes hope. Finish this sentence. After a diagnosis comes...

Dr. Rouce: Opportunity to be empowered. Ensure that you have all the information you need to buckle down and create a care team around you of friends, family, the healthcare providers to figure out the best ways to cure your cancer.

Alicia: We 100% agree with that. Thank you so much for joining us on this episode, Dr. Rouce. You are such a pillar of hope for so many patients and caregivers; and we just thank you for all you do and continue to do. We hope that we can talk to you again in the future.

Dr. Rouce: Absolutely. I would love to come on again. Thank you so much. This was amazing.

This is so important and I think there's nothing more important for me than getting the information out to patients, and caregivers, and their families. And, you know, there's only so much you can do within an office visit or a consultation and if I had it my way, I would just not leave the room until the patient or the family felt comfortable. And I would talk to every person in their life that they wanted to get their support. So, I think things like this are super important because we need them; and, you know, you guys provide an outlet that's outside of the doctor, and the hospital, and their family because, also, I note that patients feel like they are cheating on their doctor if they ask questions about another trial...

Lizette: Yes.

Dr. Rouce: ... like that. So, I love what LLS does because it allows them an outlet of knowledgeable professionals who have no, I don't want to say ulterior motive, but don't have stakes specifically in them doing something a certain way and there's no—I mean, there should be no ego in medicine, right?

Alicia: We 100% agree with that.

Dr. Rouce: That's the way.

Alicia: Absolutely.