

## THE BLOODLINE WITH LLS

A PODCAST FOR PATIENTS AND CAREGIVERS

### ***Episode: 'Attacking the Cancer Cell: Advances in CAR T-Cell Therapy'***

#### **Description:**

Please join us as we speak about CAR T-cell therapy with Dr. Carlos Silva, a Moffitt Cancer physician at Memorial Healthcare System in Pembroke Pines, Florida. In this episode, we explore the latest advances and what the future holds for CAR T-cell therapy.

This comprehensive view of CAR T-cell therapy will give blood cancer patients and their families hope. Through the utilization of targeted therapies, we can now see a future filled with better outcomes and potential cures.

#### **Transcript:**

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

Today we will be speaking to Dr. Carlos Silva, a hematologist/oncologist, bone marrow transplant, and cellular therapy specialist with the Moffitt Malignant Hematology & Cellular Therapy team at Memorial Healthcare System in Miami, Florida. He specializes in providing management of hematologic malignancies, including stem cell transplant, CAR T-cell therapy, and treatment of posttransplant complications. In addition to active clinical practice, he's involved in innovative clinical trials focused on lymphoma.

Welcome, Dr. Silva.

**Carlos Silva, MD:** Thank you for having me.

**Elissa:** Our topic today is on CAR T-cell therapy. Can you let our listeners know what that is?

**Dr. Silva:** Yeah. So, if we talk about CAR T-cell therapy, it's a current breakthrough in the management of hematological malignancies, and it becomes a part of the immunotherapy and cellular therapy approach to treat multiple blood cancers such as some lymphomas, forms of leukemia, and, most recently, multiple myeloma.

The way that this is done is primarily through a T cell that is from the patient and then those cells are engineered in the lab. They're manipulated to produce some specific chimeric antigen on the surface of those cells that will be tailored toward each patient, and then those cells will eventually be reinfused to the patient. The goal of those CAR T cells is that they will go into the body to recognize the cancer cells that they were trained or engineered for and attack the specific cancer cells.

**Elissa:** What's nice about that is that it targets the cancer cells and leaves the healthy cells alone, right? So, it's very different from chemotherapy in that way.

**Dr. Silva:** Yes. One of the major differences is that this is a specific approach, and it is one of the challenges in cancer care. Depending on which kind of cancer, it could be more challenging than others. Once it was discovered there is a particular target that could be used to attack cancer cells without causing serious consequences to the patient, it led to a specific therapy in an otherwise case that will be difficult for a patient because these therapies are used for patients that have failed multiple therapies or for which there will be no other options in the past.

**Elissa:** Now, we know that CAR T only works on some types of blood cancers. What cancers is it currently approved for and why is it only limited to certain types?

**Dr. Silva:** Since 2017, there is currently like six CAR T-cell therapies approved by the FDA, and the current target of the CAR T-cell therapy is to treat some forms of lymphoma, like diffuse large B-cell lymphoma, follicular lymphoma, mantle cell lymphoma, ALL [acute lymphoblastic leukemia], and multiple myeloma.

Then the reason for that is because, as I mentioned in the beginning, there is a specific target to identify how to attack each one of those cancers. Some of these antigens, depending on the disease, are unique for each of those entities. And these antigens are considered expendable, so technically by trying to eliminate them, they will not have any major consequences for the patient.

So in lymphoma, for example, there is the CD19 target that could be treated, and the CD19 is expressed in some of the lymphoma cells but also in some of the healthy B cells.

But despite attacking the cancer cells and some of the B cells, consequences for the patient could be tolerated. It could be increased risk of infection in the future, but it could be manageable with some medications that we have, such as IVIG [intravenous immune globulin], so there is no life-threatening potential complications in that regard.

**Elissa:** You mentioned a bunch of different cancers, but not the myeloid malignancies, correct? So, acute myeloid leukemia, chronic myeloid leukemia. Is that because we can't find the specific targets to be able to take of those cells?

**Dr. Silva:** One of the main differences regarding lymphoid and myeloid treatment and limitations for the CAR T-cell therapy, as I mentioned before, is that with the B lymphoid malignancies, the CD19 ablation or elimination of CD19 in cancers and healthy cells is tolerated. However, in myeloid malignancy, such as acute myeloid leukemia, MDS [myelodysplastic syndromes], or, as you mentioned, CML, then there is absence of that disposable antigen because they are co-expressed in the cancer cell but also in the hematopoietic stem cell. So, by attacking that, then you could have a myeloablative impact in the bone marrow that will affect the bone marrow and increase the risk of having a bone marrow failure-like state. That's one of the major challenges. In addition, that myeloid malignancies, such as AML or high-grade MDS are very heterogeneous, so in many cases then we have the tumor microenvironment

in the way that the disease pathophysiology is way more complicated, so there is multiple ways of escaping treatment.

**Elissa:** So, when oncologists are considering eligibility for CAR T, what other factors besides the type of cancer can affect the eligibility of a patient?

**Dr. Silva:** The eligibility is pretty broad. There's a limitation regarding access to care because we can estimate that only about 25 to 30% of patients that need these therapies might have access to it.

**Elissa:** Oh!

**Dr. Silva:** Access is one of the major challenges for cellular therapies currently.

**Elissa:** So is that with community health centers versus being close to a large major cancer institution?

**Dr. Silva:** It's because it's a comprehensive cancer care and when it comes to cellular therapy, such as transplantation or CAR T-cell therapy. You need to have access to the center that is established and can perform these kind of interventions and treatments and that is qualified in credential to perform them. And that already has some geographical and socioeconomic limitations for patients-

**Elissa:** Yes.

**Dr. Silva:** -in addition to where they live, their healthcare coverage; and then after that, if they have caregivers that can help them going through this. Afterwards, as we evaluate the patients, if they have overall health that would allow them to receive some of these cellular therapies.

The last part would be the time to get to the cellular therapies. Many times they do have relapsed/refractory active disease that is being controlled in different ways. But by the time the cell process, collection, sending the cells to the lab, and expansion,

and getting the product back, which on average could be around two to three weeks, in some cases could be too long for some patients-

**Elissa:** Yes.

**Dr. Silva:** -and some of them will not make it to the CAR T-cell therapy.

**Elissa:** And that's why we're looking at now potential of off-the-shelf CAR T cells or the allogeneic CAR T cells from donors and that being an option. Could you tell us more about that and why that patient might utilize the donor cells versus their own cells?

**Dr. Silva:** So that's one of the current areas that are being explored when it comes to CAR T-cell therapy in the concept of universal CAR Ts or off-the-shelf CAR T in an allogeneic CAR T setting. One of the concepts behind that is that some of the T cells from healthy donors could potentially have greater persistence than T cells from a previously treated cancer patient or it could increase the use of fit T cells, and we might shorten the time for access to CAR T cell.

But, there's still some concerns of things. Currently, Phase I studies that are looking into that. One of the studies have shown that in some cases has been safe, but we'll need to see larger studies and more data because there could be potential similarities in the management or complications, such as with allogeneic stem cell transplant, when it comes to the impact of these allogeneic T cells with the HLA matching of the patient and alloreactivity of the T cells that could be more harmful for the patient and increase risk of some complications, such as graft-versus-host disease [GVHD]. And also, in some cases, it could be potential issues regarding rejection of a foreign T cell in an alloreactive setting.

So, at this point in time, we'll need more time to find out and see how these studies progress and see the results in larger samples to know the feasibility, the responses, and the risks. I anticipate that it's going to be part of the information we'll see in the

upcoming years and see if that could become part of the current armamentarium (the medicines, equipment, and techniques available to a medical practitioner) to treat the disease.

**Elissa:** When should a patient be evaluated for potential use of cellular therapy?

**Dr. Silva:** The goal is to work with their community oncologist and identify the patient that is resistant to chemotherapy or that has failed multiple lines of therapy, depending on which disease they have. And we hope that the patient and/or their oncologist reach out to a credentialed cellular therapy center, so we can evaluate the patient early to see their indication and eligibility for a transplant and/or CAR T cell and help with these outcomes. Once we provide this intervention to the patient, we can work with their community oncologist so they can return to them to continue their follow-up and work with us with the additional steps down the road.

**Elissa:** What if a patient is not eligible for CAR T-cell therapy based on their diagnosis?

**Dr. Silva:** If they're not eligible based on their diagnosis or where they are in their lines of therapy, I still think that they should be evaluated by a blood cancer specialist to see if they have other alternatives. Whether it's a transplant or if they could have access to a clinical trial with novel therapies and/or cellular therapy with different CAR Ts. And it will be essential to get that information before coming into additional standard chemotherapies.

**Elissa:** I'm really glad that you mentioned clinical trials. At LLS, we have a Clinical Trial Support Center where patients can go and find clinical trials, come back to you and let you know that they might be eligible for a particular trial. So it's great to know that there are clinical trials out there, and we hope that patients listening will contact, at any point after your diagnosis, the Clinical Trial Support Center to look and to see what's available.

**Elissa:** So what side effects might a patient experience after CAR T-cell therapy?

**Dr. Silva:** With the CAR T-cell therapy, we have side effects that depend on the time where they are with their cellular therapies, but initially, the major side effects that we could see is cytokine release syndrome (CRS), which is a form of inflammation. As the CAR T-cells are working and attacking the cancer cells, it will release some inflammatory products in that process and that can lead to an inflammatory state for the patient. And there is different potential complications related to that that they need to be monitored in the hospital for.

And then, they could also have some side effects called neurotoxicity related to that that we call ICANS or immune effector cell-associated neurotoxicity. And there is different degrees of that, so it can cause some confusion or increased risk of a seizure and altered mental status. If it's detected and managed appropriately and early, it tends not to cause very serious complications.

And there's also some side effects related to the chemotherapy used before the CAR T cell is administered that is called a lymphodepletion chemotherapy. It's a chemotherapy used to just lower some of the patient's own immune system to allow the CAR T cells to go in and work and expand; and in that way, attack the specific cancer. They could have increased risk of infection and low blood counts for a period of time. In some cases, that might require blood transfusions.

Sometimes, we can see months later that these patients lost some of their B cell function and they can have an increased risk of infection, like sinopulmonary infections if they have a low immunoglobulin or hypogammaglobulinemia that can be monitored and prevented with IVIG infusions. Those are the most common or significant side effects associated with CAR T-cell therapy.

**Elissa:** Is CAR T a first-line therapy? So, after a diagnosis, is it ever the first treatment that is given to a patient?

**Dr. Silva:** It is not at this moment in time. At this moment, it still remains a salvage option and depends on which disease we're talking about. It's always in the case of refractory and/or relapsed setting. In many cases, after multiple lines of therapy. Whether in some cases, such as diffuse large B-cell lymphoma, if it's the refractory disease or if patient fails the first chemotherapy regimen or relapses in the first year versus patients that have failed, let's say two lines of therapy, or in multiple myeloma patients that have failed after the four lines of therapy. So, it hasn't become and is not the first-line therapy.

There's some studies that will look into that to compare standard of care first line chemoimmunotherapy versus a CAR T cell-

**Elissa:** Yeah.

**Dr. Silva:** -and see probably responses and compare them, hopefully in the future, to see duration of response and if these patients relapse, what the differences are and what options we'll have after CAR T. So, we will find out more in the future.

**Elissa:** Speaking of the future, we have really just come so far with CAR T-cell therapy, particularly in this past decade. Where do we see CAR T going in the future? Are we going to see more blood cancer types approved or do you think we could see it as a first-line therapy at some point?

**Dr. Silva:** I think it's early to know. As I mentioned before, then we'll need some of these studies to happen-

**Elissa:** Yeah.

**Dr. Silva:** -to mature and see what the data shows. I think one of the take-home messages is that there is hope because there's certainly multiple treatments that are available and so many that have been approved in the past decade that were not available and we have them now. So, now is just to find out more and work more on the current best therapies to see how can they be improved, how can they be more



effective. Or how can you develop a new cell, in this case let's say a CAR T cell, and dual target to see patients that lose their target with the CAR T, and now can we target the cancer in different parts that it hasn't been targeted yet, the new antibodies.

There's definitely hope for new therapies and to find out how we can incorporate them and how to time them better for these patients. It's a very exciting time as a cellular therapy doctor and also for the patients. And we hope that as everything continues to progress, hopefully, we can increase the access for patients so they can also receive these therapies in an easier way.

**Elissa:** Wow! That is just really exciting. There's just so much hope for the future. And now speaking of hope, our last question today. On our patient podcast, we have a quote that says, "After diagnosis comes hope." What would you say to patients and their families to give them hope after a blood cancer diagnosis?

**Dr. Silva:** I think that to give them hope is essential that they understand the disease and what's going on and that they obtain information from reliable sources. I advocate for The Leukemia & Lymphoma Society website, [LLS.org] so they can obtain education about the disease, also to learn about patient experience and see the options for them and their caregivers. That way they can have some sort of support behind them. It's essential to have support in order to go through all these cancer treatments we can provide because it's certainly challenging-

**Elissa:** Yeah.

**Dr. Silva:** -and it's not easy physically and mentally. But I believe that there is hope as we have many therapies available we didn't have before with even new chemotherapies, new targeted therapies, new antibody therapies, cellular therapy. I think that is likely that, because of the current data and tools and technology, we will see more new therapies in the upcoming five years. It's a good time for these diseases, and we hope that it might translate into more options for other forms of blood cancer.



**Elissa:** Wonderful. Well thank you so much, Dr. Silva, for joining us today. We really appreciate you sharing all about CAR T therapy and the potential for the future and how we might be able to see use of CAR T with more blood cancers and some success. Thank you so, so much for being here with us today.

**Dr. Silva:** No, thank you. It's been my pleasure.

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

To help us continue to provide the engaging content for all people affected by cancer, we would like to ask you to complete a brief survey that can be found in the Show Notes or at [TheBloodline.org](http://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.

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

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](http://LLS.org/PatientSupport). You can find information about CAR T-cell therapy at [LLS.org/CARTTherapy](http://LLS.org/CARTTherapy). All of these links will be found in the Show Notes or at [TheBloodline.org](http://TheBloodline.org).



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