

THE BLOODLINE WITH LLS

A PODCAST FOR PATIENTS AND CAREGIVERS

Episode: 'Cellular Revolution: CAR T-cell Therapy'

Description:

Explore the cutting-edge of oncology as we delve into the revolutionary world of CAR T-cell therapy, a more recent medical advancement in the fight against blood cancer.

Join our conversation with Dr. Marco Davila of Roswell Park Comprehensive Cancer Center in Buffalo, NY, as he highlights the significant impact CAR T-cell therapy has made on treating various blood cancers. Dr. Davila discusses the current uses of this therapy and gives us a look at the ongoing clinical trials that are broadening the horizons of this innovative treatment.

Transcript:

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

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

Elissa: Today, we will be speaking to Dr. Marco Davila, a hematologist/oncologist and the Senior Vice President and Associate Director for Translational Research in the Department of Medicine at Roswell Park Comprehensive Cancer Center in Buffalo, New York. In this role, he helps lead a comprehensive program encompassing all aspects of cell therapy for cancer. While a clinical fellow at Memorial Sloan Kettering, Dr. Davila helped to develop some of the first CAR T-cell therapies for patients with blood cancer. Welcome Dr. Davila.

Marco Davila, MD: Hi, thank you.

Elissa: So, Dr. Davila, let's discuss CAR T-cell therapy. Could you tell our listeners what that is and why this treatment is so ground-breaking?

Dr. Davila: Sure. For a long time, investigation of the immune system kind of held that its main functions were to treat infections, things like bacteria, viruses, and fungi. There was always some debate though that whether the immune system had a role for preventing and treating cancer.

Eventually, investigators such as Dr. Steve Rosenberg out of the National Cancer Institute showed that T cells can infiltrate in cancer; and if you take them out and expand them and put them back into patients, that this can actually lead to resolution of their disease. So, this was really some of the best evidence that T cells, number one, have that ability to be able to identify cancer and number two, have the ability to be able to treat and cure cancer. So, CARs (chimeric antigen receptors) are an innovation upon that idea because taking T cells out, expanding into large numbers, was very cumbersome. It would take months sometimes and sometimes wasn't successful at all.

And part of this was because these tumor-infiltrating lymphocytes, the TILs that Dr. Rosenberg identified had tumor reactivity built into them so, they had to be expanded to large numbers before they got put back in. But CARs were an innovation because essentially it used gene therapy to be able to put that tumor reactivity within each T cell.

So, T cells could be isolated from patients, from their blood. It was a very simple procedure in apheresis. In doing gene therapy, they're able to put a gene into these T cells, what essentially allowed them to identify the cancer and to also kill the cancer at the same time. So, it created this process that instead of taking months, could take as short as two weeks. And now some groups are doing it as short as one day, for example.

Elissa: Oh!

Dr. Davila: So, this has been the big innovation of cell therapy going from things like TILs to now CAR. So, essentially a combination of both gene therapy as well as cell

therapy; using the innate ability of T cells to be able to kill cancer cells but, using gene therapy to be able to help them identify what to kill and how to kill it.

Elissa: So, is the benefit of modifying the T cells really to go in and use that targeted therapy towards just the cancer cells versus chemotherapy where you come in and kind of kill everything?

Dr. Davila: Yeah. There's probably two or three benefits built into the CAR itself. So, the gene therapy is basically CAR. CAR stands for chimeric antigen receptor. It's the chimera, or two parts, because part of is an antigen-binding domain that's usually derived from an antibody, fused to signaling elements of a T cell receptor.

Within this CAR, it has two or three critical components. One is it helps it to identify what to kill, and that provides its specificity. That doesn't necessarily mean that it doesn't kill noncancer cells because sometimes other cells also express that target.

So, the first FDA-approved CAR T-cell therapy was a CD19-targeted CAR. CD19 was chosen because it's expressed on nearly all B cell malignancies. But CD19 is also expressed on normal B cells. And so, it was something that we anticipated when we were developing this that if this works, patients may develop B cell aplasia, meaning that their normal B cells will be depleted. And they could have infectious issues after treatment with CAR T-cell therapy.

And it's something that we've seen in patients, that we can see a drop in their B cell counts. But luckily, the CAR T cells don't seem to persist forever in most patients and B cells do recover over time in presumably their infectious response.

Also, within the CAR includes the signaling elements for the T cell receptor. So, this tells the T cell to activate and to kill its target. And they include other genes as part of this receptor, co-stimulatory genes, that endow better features to the T cells. So, the ability to be able to expand and also to persist longer term.

And what's kind of cool about this is this is the designer gene. So now we can put other things into this gene as well to maybe, help the T cells expand even more, persist longer, or to traffic to different organs.

So, this is generation 2. So, generation 1 never really worked that well in patients, so that's when the co-stimulatory genes were added in. We're at gen 2, so now what we're excited about is looking at things like gen 3 or gen 4 to go. How can we get even better outcomes against different diseases for patients?

Lizette: Wow. And Dr. Davila, what blood cancers is CAR T-cell therapy currently approved for?

Dr. Davila: A lot, and the list keeps on growing and the indications keep on improving and changing.

So, the first approvals were in the fall of 2017 for children with acute lymphoblastic leukemia (ALL), later for adults with large B-cell lymphoma. Since then, there's been approvals for mantle cell lymphoma, follicular lymphoma, and now multiple myeloma.

What's really cool though is that those initial approvals were for patients with multiple relapse disease. So now, clinical trials have been done and supported the use of CAR T-cell therapies at an even earlier line. So, for example, aggressive B-cell lymphoma or large B-cell lymphoma can be used in patients as early as second line. So, they get R-CHOP chemotherapy, they get in remission. And if the disease comes back quickly, instead of going onto other therapies, these patients can proceed directly to CAR T-cell therapy.

That's good because we think, in general, you move things up earlier, the outcomes get better. But also, the patients are a little more fit; and the toxicities are a little less. So, that's been an important recent change within the approvals.

Lizette: Sure. And are there CAR T-cell therapy clinical trials for the other types of blood cancers?

Dr. Davila: Absolutely. So the main, remaining hematologic malignancy that does not have indication for CAR T cell is myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML). Those have multiple clinical trials looking at targets such as CD33, CLL-1, CD123. We have one against CD83. So, these are all multiple different clinical trials are happening all over the United States and the world.

Elissa: Okay. Now outside of having a cancer where the therapy is approved, what are the eligibility requirements for CAR T-cell therapy?

Dr. Davila: So, they're very actually minimal. So, it's diagnosis and lines of therapy. So, those are the two main things that let us know is a patient eligible for CAR T-cell therapy.

That being said, there are other things that we do in our workup to be able to evaluate the risk that this patient might have for a complication. So, we have published in collaboration with colleagues from Europe as well as from the Moffitt Cancer Center, that inflammatory biomarkers such as CRP and ferritin, when they're elevated, identify patients at a higher risk for a toxicity or an early death from progressive disease.

So, we don't use this type of information to say you shouldn't get a CAR T-cell therapy. We use it to be able to go, "Well, maybe we should give you prophylactic medication to reduce the risk of some of these toxicities." Or sometimes it helps us identify a CAR T-cell product associated with lower toxicities for this particular patient.

Those are the ways we use it. Or, we might use this information to say, "You know what, I'm not sure if the standard of care product is best for you, but a clinical trial could be a better option for these patients." So, we use this information not to necessarily rule patients out for CAR T-cell therapies, more to kind of figure out what's the best way we can give those patients so that we maximize their potential for a good outcome?

Elissa: You talked about lines of therapy. Is CAR T used as a first therapy; or is it often mostly then used after a patient may have relapsed or tried other treatments that didn't work?

Dr. Davila: Is it a frontline or first-line therapy? The answer today is no. That answer could be different though in a few years. There are clinical trials open right now that are looking at patients at high risk for relapse after first-line therapy and going, "Well, let's give them a CAR T-cell therapy as consolidation or in combination with that first-line therapy."

So, we're hopeful that this could potentially be a first-line or frontline therapy within a few years, but right now it's not.

Lizette: And what are the common side effects a patient might have after CAR T-cell therapy? Are they really different from other treatments like chemotherapy or even stem cell transplantation?

Dr. Davila: Yeah, absolutely. So, as you were discussing in the intro, I was involved with probably one of the first clinical trials investigating viral-transduced CAR T-cell for patients with cancer. We think it was quite possibly the first in the world.

And when we wrote the clinical trial, you have to think about things like adverse events and dose-limiting toxicities. So, we really describe adverse events and dose-limiting toxicities that are associated with acute lymphoblastic leukemia, getting treated with chemotherapy. So, things like, infections, low counts, nausea and vomiting, and things like that. So, we had never even anticipated the types of toxicities that we encountered. They were essentially a new form of the cancer therapeutic toxicity.

And so now we kind of, know how to describe them, know how to diagnose them, know how to manage them in a much better way than we did when we first opened these trials in 2006 and we'll continue to refine this. So, when I speak with patients, I say, the two initial toxicities that we look for in patients that are associated with the

CAR T-cells is the cytokine release syndrome, or CRS, and a neurologic toxicity, which is also commonly referred to as ICANS or immune cell-associated neurologic syndrome.

And so, these are toxicities that, in general, occur within that first one to two weeks post-CAR T-cell infusion. The kinetics, the median onset, the duration can vary from product to product but also can vary based on things like, tumor burden, for example, within the patients.

And so, the cytokine release syndrome, I generally describe as a fever-based toxicity. So, it can feel like the worst flu of your life. Patients will develop high-grade fevers, malaise, and will just not feel very well. And that's kind of just a low-grade CRS.

When it starts increase in severity, they can start having cardiovascular complications, things such as hypotension and hypoxia; and that's actually part of the grading system. So, if you have evidence of hypotension or hypoxia, you go from a Grade 1, which is fever alone to Grade 2. And if it's not responsive to intervention, you kind of keep on escalating grades. And when we initially developed these technologies in these clinical trials, we were worried that interventions might worsen the CAR outcome, so we would always wait until the patients were the most sick before we would intervene, such as Grade 4.

But now through lots of clinical investigation reporting, we know you can intervene pretty much as early as Grade 2 and improve the safety of the technology pretty significantly and not necessarily worsen the overall clinical outcome. You won't worsen the biologic efficacy of the CAR T-cells. So, that's the cytokine release syndrome or CRS.

Another, toxicity, ICANS, is a very heterogeneous syndrome of toxicities. So, it can sometimes be as simple as just a headache. Sometimes you might have mild tremors. I think one of the more common presentations are word finding difficulties. Patients you can speak with them. It's one of those things where anytime I have a concern, I just speak to the patient, ask them a lot of questions. Seeing how quickly they're able

to respond to some of these, and you're seeing these patients in the hospital every day. You can kind of notice that difference. So, sometimes the patients would be completely aphasic, and/or obtunded, or have grand mal seizures.

So, it's the same thing here. Low-grade toxicities such as Grade 1. Really, we just let the patients provide supportive care. But once it becomes more severe, a Grade 2, Grade 3, we try to intervene.

So, those were the big two acute toxicities that we monitor for. Now, there is an appreciation that there's some longer-term toxicities that can be associated with this. One is the one that I talked on initially, B-cell aplasia. Low immune cell counts, which can make the patient susceptible to infections.

So, it's even gone a little bit beyond B-cell aplasia. We can see that patients can be cytopenic, so they can have low neutrophil counts. They can have low red blood cell counts, and you can be anemic in addition to being neutropenic.

So about 20% of patients can have these long-term cytopenias. This can put the patients at risk for infection. So, in general, the way we manage those is aggressive antibiotics, IV, intravenous immunoglobulin to help support them if they do develop infections. But as well as sometimes growth factor support, things like PROMACTA® to see if we can stimulate platelet recovery under G-CSF (Granulocyte colony-stimulating factor) to stimulate neutropenic recovery.

Most patients will recover over time, like six months to a year. Some patients, those with multiple myeloma can actually benefit from a stem cell infusion. So, as part of the normal process for patients with myeloma that everyone pretty much gets an auto[logous] stem cell transplant, sometimes patients even get two auto stem cell transplants. So, the general practice is you collect enough stem cells for these patients to do two stem cell transplants.

But nowadays, patients don't get a second stem cell transplant. They get a CAR T infusion. So, we've had some patients that have low counts afterwards that we just do a stem cell infusion, and that fixes the pancytopenia within a month.

So, those are probably the three main toxicities. This third one, is probably the one that we worry about a lot now since we feel pretty comfortable managing the first two in the hospital. We have good management schemes. We keep on refining this.

The number two killer of patients, the number one being their disease coming back, is infections. So, this cytopenia is a major area of investigation; and we're working. And many times like patients that come here to see us, they live far away, so we really have to partner with their primary care providers or primary medical oncologists to be able to identify these patients and give advice on how they should be managed and sometimes, bringing them back here to do workups and stuff like this.

There has been some reports. I want to be, mindful of at least discussing this. The label has changed for some of these products recently, where they talk about the potential risk for another malignancy for some of these patients. There's been reports that some of these patients that developed T-cell lymphomas, for example. And when it was first announced, that got a lot of people's attention because what we were afraid of, there's this other kind of risk. So, these were things that when we were designing these products, we said, "What are we going to be worried about? We're going to be worried about, B-cell aplasia, on target/off tumor toxicity.

The other thing we were worried about, was this thing called insertional oncogenesis. So, sometimes when you use the virus that you use to put these CAR T cells, if they integrate into a bad spot, it can actually lead to the T cells, instead of becoming a CAR T cell, becoming actually T-cell lymphoma.

This had been seen not with CAR T -cells, but with a stem cell treatment, where patients in Europe were treated with a gamma-retroviral modified stem cell to try to correct their immune deficiency. And the patients developed these T-cell leukemias

and lymphomas shortly after the treatment. So, it's something that we knew could happen, we were worried about.

But luckily, it's been reported now people have gone back. They looked at major databases. They looked at their patient experiences. While patients can develop T-cell lymphomas, it doesn't appear to be what we were worried about in terms of something associated with a CAR insertion event and then, a transformation of that T cell due to that CAR insertion.

That doesn't still mean it's not possible. There is a risk. We just don't know what the denominator of that risk is. But since the first CAR was approved in 2017 and we're seven years afterwards, it still haven't necessarily defined many cases of this potential outcome. We think it's something that's very, very rare and likely the patients facing a cancer that will likely kill them within months, it becomes a very good kind of risk-benefit calculation for the patients. But those are things that we talk about in patients. So those would be the main toxicities.

Lizette: Right. And you mentioned that people are in the hospital for most of these toxicities. Do you still see the patients in the hospital? How long are patients in the hospital after treatment?

Dr. Davila: This is changing. So, initially, we kept all the patients in the hospital. With these first clinical trials, we would have patients go straight to the ICU because we were worried about them getting sick.

But, now you can do this outpatient with some of the products. So, we'll do early discharges on some of these patients, discharge them as soon as day one and say come back. There's some products we can even outpatient. So, some of these products, the median onset of the toxicity isn't until day 6 or day 7. So why do I want to keep a patient in a hospital, waiting for them to get a toxicity if this might be a week or something like that?

So, we'll send patients out and if they get a fever, they're monitoring their vital signs at home, they have a caregiver 24/7, they have an issue, they come back in, we admit them, and we manage the toxicity. So, it's dependent on the patient and dependent on the product. You can do this inpatient or outpatient.

Lizette: Okay. We know that a lot of folks that get stem cell transplantations, specifically more allogeneic stem cell transplantation, have to stay in the hospital for a while or have to be within a certain distance of the hospital just because of the possibility of certain toxicities. Is that the same with CAR T? If you're sending people home, do they have to be in a certain area to get back to you?

Dr. Davila: Yes. So, part of this is regulated by the FDA and the pharmaceutical companies REMS (Risk Evaluation and Mitigation Strategy) programs. So, in general, I think the criteria is something like they have to be within 2, 2.5 hours of an authorized treatment center, or ATC. They have to be seen by a provider for 7 days, daily after that infusion.

And I think our policy is we want patients to be kind of within that distance for about, 28 to 30 days. But again, I always try to treat the patient in front of me. You know, going, the patient had very low risk for toxicities, had no toxicities, in Syracuse, which is about a couple hours away from me. I would feel comfortable with them, leaving the closest city to Buffalo to go back home.

It's more comfortable. I always tell patients the goal of this treatment is to return you back to your life. It's not to make you a prisoner for our own concerns or anxieties.

Lizette: So, the aftercare of CAR T-cell therapy, is that shorter than something like stem cell transplantation?

Dr. Davila: Yeah, I think so. In general, our policy is we try to get patients back to their primary medical oncologist around two to three months after their CAR T infusion. So, around two to three months afterwards, we do kind of restaging PET scans and/or

bone marrow if indicated, things like that. We want to see what their response is and then get them back to their medical oncologist.

They still may have evidence of cytopenia, so, I'll speak with the medical oncologist. So, this is the way we manage it. If you just want to send them back to us every once in a while to keep an eye on them to give you advice, happy to do that.

But our goal is really for the patients to go back two to three months; and to be honest, that should be when these patients are, returning to their life. If they have no residual toxicities, they should, feel comfortable with returning to work or doing the activities that they love. So, that's not just our goal for them going back home but really to returning to their life.

Elissa: Now, you mentioned the restaging tests to check on the results of the CAR T-cell procedure. What are you looking for to see if the CAR T was successful?

Dr. Davila: So, that's also a little kind of difference from the stem cell transplants that you talked about before. So, like allotransplants (allogeneic). You go into an allotransplant in a complete remission. So, when you restage them, you want to make sure they're still in a complete remission and have no evidence of things like graft-versus-host disease (GVHD).

With the CAR T-cells, they may have, minimal residual disease, they may have, like 10% blasts within their bone marrow if it's ALL. They may have, a few spots of lymph nodes that are increased in size or massive lymphadenopathy. So, really what I want to see around that three-month point in time is that they have no evidence of disease, that I can classify them as a complete remission (CR).

Most patients that have good responses, you would expect them to be in a CR, by around three months in time. So, that's really what I'm looking for. If they have a PET, no evidence of metabolic disease. If they have a bone marrow, no blasts greater than kind of 5% or no malignant cells, that meet the diagnostic criteria. So that's what

I'm looking for, but we do those other things to kind of look at what are their immunoglobulins? You know, are they B-cell plastic? Are they going to be susceptible to infections? Because when we hand everything back off, we want to be able to give that information to their medical oncologist.

Elissa: Dr. Davila, we'd love to hear about where CAR T is going in the future. Are there any emerging therapies? Are those in clinical trials that you're particularly excited about?

Dr. Davila: Yeah, I mean there's a lot of different direction. So, when we opened that first trial in 2006, probably the number of CAR T-cell clinical trials that are developing over the next few years you could count on one or two hands. And now, there's hundreds and hundreds of trials.

So, there's just a lot of investigation going on that's not just in terms of efficacy. So, the way I want to think about this, where's the need and what are some of the exciting or cool technologies?

Where the need is very clear. Acute myeloid leukemia and solid tumor malignancies. Acute myeloid leukemia, that's kind of a natural, next kind of focus; but really the need is solid tumor malignancies.

There's a solid tumor microenvironment which is very, very inhospitable. So, part of my research has always been, I really want to focus on these hem malignancies because, they work about half the time. So, why they don't work in that other half, I think, is going to be very, very informative of us as we translate these technologies to solid tumor malignancies.

My colleagues and I have identified things like myeloid cells, macrophages within the lymphoma microenvironment that are playing major roles of resistance. So, those are things that when we start applying these technologies to solid tumors, we're not going

to do just Gen (Generation) 2. We're going to do Gen 3, which somehow also focuses on macrophages, as something that we need to address.

So, that's where the need is. Now, what are the exciting technologies? One is off-the-shelf work using allogeneic CAR T-cells. So being able to have to collect T-cells from patients, send them to a facility for engineering, we've gotten better at that; but it takes, in general, two to four weeks in time. And what's crazy is that one to two weeks of that time is probably just testing to make you sure the product is safe to infuse back in the patient.

So, even as we've gotten the production time short as one or two days, the turnaround time still can be two weeks for some of these products because of all the testing. Allo CAR T-cells address that, so in theory you could potentially infuse the patient the very next day with a product. So, those clinical trials have been going on for five years, but they're dealing with the problem of rejection. That even a patient with cancer, their immune system is still good enough to be able to recognize the CAR T-cells as foreign and rejecting them.

They see good responses that match those of auto CAR T cells or the standard CAR T cells. But, they don't match the durability. The patients are relapsing at a higher rate than with an auto-CAR product. So, they're going back to the drawing board to figure out how to kind of improve that. But that's something that as a provider of these technologies, I'm very excited about because I really feel this would benefit patients greatly.

And the other is going, well, where do CAR T-cells go next? Now people are actually applying this for noncancer indications. So, rheumatologic diseases, autoimmune diseases are the ones that people are really, really excited about. So, things like multiple sclerosis, Sjögren's, lupus, diseases that really don't have very good therapies or when the patient stops responding to them, the options for the patients become very limited.

So, we're really excited about that. And, obviously, I'm excited about my own work. So, we're going to be opening a clinical trial for CD83 for acute myeloid leukemia within the next few months.

So, those are the things we're really excited about; but, that's just a drop in the bucket. There's a lot of stuff that's going on all over the world; and each time I go to a major meeting, I'm excited because I'm going to see something that, I never even conceived of. And, it's what happens if you have a lot of bright people that really see the potential in this field and applying their ideas to this technology.

Elissa: For some blood cancers, do you see CAR T-cell therapy potentially being curative?

Dr. Davila: I think for B-cell malignancies, we consider them to be having the potential to cure patients, absolutely. Myeloma, the jury's still out. We see some patients, we see some curves that are still plateauing. They're not continuing to go down. So, we think that potential may be there, but what's clear is, I think, when I speak with patients to say, why are you here? Because sometimes they might hear about the toxicities. Sometimes I might hear, "I have to see a doctor every day for 7 days and be here 30 days."

I said, "Hey, listen, when we get on to that, but the first thing I want to say is that right now this therapy has the potential to cure you." That's my goal. That's why we're recommending this is that we think this might cure you. For some patients, that's the only curative option available for them.

So, then I think the patient kind of understands. Okay, well, these are inconveniences, annoyances. But, this is not something that's going to improve my overall survival by six weeks, right? This is the potential to give me my life back.



So, there's that. In myeloma, we'll see. I mean the first approvals ever out there, I'm hoping at this earlier lines of therapy, we're going to, maybe have enough data to be able to say it for some patients it can be curative.

Elissa: That would be great.

Our final question today, on our patient podcast home page, we have a quote that says, "After diagnosis comes hope." Dr. Davila, with the latest advances in CAR T-cell therapy, what would you say to patients and their families to give them hope after a blood cancer diagnosis?

Dr. Davila: I say, "As a medical oncologist, I'm always hopeful." Every patient that comes into that room, I'm hopeful. I'm optimistic that there's something that can provide to you that's going to cure you of your disease and can get you back home with your family doing the things that you love.

And even if it's not entirely curative, it's going to improve, the quality and the quantity of your life. So, I always try to find ways to be positive and to figure out ways with the patient how we can make this a success for them.

Elissa: That is so good to hear.

Well, thank you so much, Dr. Davila, for joining us today. I think this was a wonderful discussion all about CAR T-cell therapy and where it could go in the future for blood cancer patients. And so, we really appreciate you joining us today.

Dr. Davila: Awesome. I had a great time, thank you.

Elissa: 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 patients and their families.



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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.

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