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Emerging Frontiers: CAR T-Cell Therapy for Solid Tumors in Thyroid Cancer

Dr. Birnholz:

This is *Project Oncology* on ReachMD, and I'm Dr. Matt Birnholz. Here with me today to talk about his research into CAR T-cell therapy's emerging role for solid tumors in thyroid cancer is Dr. Saad J. Kenderian, a hematologist and Assistant Professor of Oncology, Immunology, and Medicine at the Mayo Clinic in Rochester, Minnesota.

Dr. Kenderian, welcome to the program.

Dr. Kenderian:

Thank you. Thanks for having me.

Dr. Birnholz:

So why don't we level set on CAR T-cell therapy just to start and get your topline thoughts on the impact that it's been making in the treatment of blood cancers from your vantage point. What can you tell us?

Dr. Kenderian:

Yeah, certainly. So I think CAR T-cell therapy has been truly revolutionary in blood cancers. As you know, CAR T-cell is a form of immunotherapy where we take the patient's own T-cells, own immune cells, they are sent to the lab to be engineered to express the CAR, and they become CAR T. That process takes anytime between five days and two weeks, and then they are sent back to the patient, and patients receive low-dose lymphodepleting chemotherapy really to make room for the engineered CAR Ts, and then that is followed by the CAR T-cell infusion. And in blood cancer, what we're seeing is that a percentage of patients go in complete remission, and this complete remission is a durable complete remission that is lasting years after CAR T-cell therapy. And following these complete remissions, the CAR Ts persist and, in some cases, persist for years and years. In the first patient that received CAR T in 2010, the CARs are still around. It was reported a couple of years ago at 10 years follow-up, and the CAR Ts are still around, and the patient is still in remission. So we're seeing long-term remissions following CAR T-cell. Arguably, some patients are cured after a single infusion of CAR T-cell therapy, so it really has changed the treatment landscape of hematological malignancies.

Dr. Birnholz:

So, Dr. Kenderian, you talked about that paradigm shift that you're seeing. Are you seeing this translating into a paradigm shift in real time over at Mayo Clinic for you and your colleagues when you're treating patients using CAR T-cell therapy in the hematology setting?

Dr. Kenderian:

We sure are. And what's remarkable and rewarding to us is that after CAR T for patients that go into complete remissions, patients tell us that, you know, "We haven't felt this way since we were diagnosed with cancer." You know, "I'm feeling back to where I was before I had the cancer diagnosis decades ago," for people who have chronic diseases like chronic lymphocytic leukemia or multiple myeloma. The goal in blood cancers is that not all patients are going into complete remission. The rate of complete remission is different from one blood cancer to the other, and it ranges between, say, 30 and 40 percent, 30 and 50 percent. These are patients that go in long-term complete remission. And the challenge is understanding what's happening, what's inhibiting CAR T, and how can we increase these remissions so that the majority of or all patients can go in complete remission and have this benefit from CAR Ts.

Dr. Birnholz:

Hmm, I think that provides a great segue for us to dive into your research to help address some of those challenges and develop this technology for solid tumors and thyroid cancer in particular. First, what led you and your colleagues into this particular direction?

Dr. Kenderian:

Yes, that's a good question. So what we are learning in solid tumors with the CAR T trials is that there are two big challenges. One challenge is there are no good antigens to target in solid tumor. Unlike in blood cancers, we have CD19, CAR 19, and we have BCMA that are uniquely expressed on cancer cells, and they don't have much expression on normal tissue. In solid tumors, the antigens are shared between the tumor and normal tissue, so that is one challenge. And then the second challenge is that the tumor itself is a mass, and it's filled with other immune cells, inhibitory cells, which form the tumor microenvironment, and that inhibits CAR Ts from getting into the tumor and from working as well as they should. So what we are aiming to do is to learn from blood cancers what's inhibiting CAR T and take that knowledge and apply it to solid tumor.

We started working with thyroid cancers. We have established models for thyroid cancers through a collaborator in Mayo Clinic Florida, Dr. Al Copland. Using these models, we identified an antigen: the thyroid-stimulating hormone receptor, or TSHR, which is uniquely expressed on thyroid cancer and does not have expression on normal tissue because it's specific to the thyroid cells. So that led us to push this further and develop a CAR and develop therapy against this antigen and test these therapies in the preclinical models.

Dr. Birnholz:

Well, for those with tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Matt Birnholz, and I'm speaking with Dr. Saad J. Kenderian about the potential applications for CAR T-cell therapy against solid tumors, such as thyroid cancer.

So, Dr. Kenderian, getting back to what you were just referring to on the protein targeting and the antigen targeting that you looked into and were able to identify regarding TSHR for thyroid cancer as a unique marker, what do you think is going to be needed to help exploit that target or even identify others going forward to make CAR T-cell therapy more effective?

Dr. Kenderian:

Yeah. So I think that one challenge is identifying targets for other solid tumors. There are not many uniquely expressed targets on solid tumors, but there are a few, and these are being pursued. So that is one challenge, and several other groups are trying to identify that through proteomics assays and through different multi-omics approaches. And then the other challenge is making CAR T more effective compared to blood cancers because the tumor has its own suppressive environment.

Dr. Birnholz:

And let's talk about that environment because I imagine issues of tumor heterogeneity play into and complicate the use cases for CAR T-cell therapy. Can you speak to that?

Dr. Kenderian:

Yeah, absolutely. Tissue tumor heterogeneity is a big factor, even in blood cancers, but more so in solid tumors. You need a target for immunotherapy that is expressed on all cancer cells. That's one of the challenges we had with thyroid cancer is when thyroid cancer metastasizes and becomes more aggressive, they lose the expression of the TSHR, the antigen that we are targeting. That creates more heterogeneity. We've identified that if you block the MAP kinase inhibitor with the small molecules—these are MEK inhibitors and BRAF inhibitors that are in the clinic but are FDA approved for thyroid cancer—but if we use them and we block the pathway, we are able to upregulate the TSHR, the thyroid-stimulating hormone, and that increases the efficacy of CAR T-cells. So in a way, we're using this strategy to overcome the tumor heterogeneity that is a result of the metastatic cancer and differentiation of the thyroid cancer.

Dr. Birnholz:

And, Dr. Kenderian, is that intertwined with or separate from the issue of tumor resistance that you've written about saying it truly factors into the picture here as a complicating factor as well?

Dr. Kenderian:

Yeah, that's another complicating factor. That is somewhat separate from the tumor resistance. For example, thyroid cancer is heavily infiltrated by the tumor-associated macrophages, and these are suppressive cells that the tumor uses as a defense mechanism, as an escape mechanism, and we're working on ways to overcome this and to block the tumor-associated macrophages to make the CAR Ts even more effective. Our goal is to move our TSHR CAR T to the clinic in combination with the MEK and BRAF inhibitors in the first

cohort, and then as we advance further, incorporate other strategies to make the CAR even stronger to overcome this infiltration by macrophages.

Dr. Birnholz:

And I understand that you and your colleagues and, of course, many in this field are monitoring how to address the risks of side effects with this treatment approach. What are you and your team on the lookout for specifically?

Dr. Kenderian:

Yeah, absolutely. So CAR T-cell therapy has unique side effects. It has side effects that come from targeting the antigen. So, for example, with CAR19 you are killing CD19-positive cells, and with that, you are killing the patient's own B-cells, and that results in low immunoglobulins and hypogammaglobulinemia, but we can replace that with immunoglobulins. So the same thing with thyroid with TSHR. We expect to kill the TSHR-positive cells, but there are not any TSHR-positive cells. There are TSHR on the normal thyroid tissue, but most patients, by the time they have metastatic disease, they don't have the thyroid tissue anymore. They've had surgery, and that was removed.

But then there is a unique set of side effects that come with CAR T that we watch for patients in blood cancer and patients in solid tumor as the CAR T-cell therapy becomes more advanced. Some of the unique side effects are the development of cytokine release syndrome, or CRS. What happens is these CAR T-cells are a living therapy, so when you give CAR T-cells to patients, CAR T-cells see the tumor, and then when they see the cancer cells, they proliferate and decrease in number by thousands and thousands and folds. And then when they do that, they produce cytokines to kill the cancer cells, and during this time, patients can get sick. They can have fevers, low blood pressures, or pulmonary edema fluids in the lung. They can have fluid overload. They sometimes need to be in the intensive care unit briefly. The good part is that these side effects seem to be driven by the myeloid cytokines, especially by IL-6. It's a cytokine that the myeloid cells make. And then when we block IL-6, we are able to prevent it or reverse this syndrome in almost all cases.

Another unique side effect with CAR T is the development of neurotoxicity or what we refer to now as ICANS, immune cell-associated neuroencephalopathy syndrome. And this is a syndrome where patients can get confused. They have encephalopathy. Most of the time it's reversible. We use steroids to help with this syndrome. Steroids may help. We don't really have very effective treatment for the neurotoxicity. Overall, clinicians are getting better in managing these side effects, and they remain, for the most part in the vast majority of patients, fully reversible.

Dr. Birnholz:

Well, let me close with that theme of working towards getting better, and let me ask you about the roadmap that you see in front of you for the next steps in your research. You mentioned some of the stages and steps that you're envisioning. Can you take us through that?

Dr. Kenderian:

Yeah, absolutely. So for the thyroid cancer, we are planning to move the TSHR CAR T into a new phase 1 clinical trial in combination with the MEK and BRAF inhibitors. And, in parallel, we are working on targeting components of the tumor microenvironment that we have worked on and published on in blood cancers and applying that in thyroid cancer.

I think in a big picture, we're going to continue to learn from what's causing failure in CAR T in blood cancers, take this, develop new strategies, and apply it for both blood cancers and solid tumors to make CAR Ts more effective and safer and benefit more patients, both with the blood cancers and solid tumors.

Dr. Birnholz:

With those forward-looking thoughts in mind, I very much want to thank my guest, Dr. Saad Kenderian, for joining me to share his research updates on CAR T-cell therapy in solid tumors, such as thyroid cancer, and the emerging work and research that he and his colleagues are undergoing to advance that cause. Dr. Kenderian, it's fantastic having you on the program. We're going to have to have you on again to talk about the phase 1 research and next stages therein.

Dr. Kenderian:

Thank you very much. Thanks for having me.

Dr. Birnholz:

For ReachMD, I'm Dr. Matt Birnholz. To access this and other episodes in our series, visit *Project Oncology* on ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening.