Personalized Vaccines Combat Melanoma

PODCAST 28

00:48
Dr. Jane Caldwell
Today *On Medical Grounds*, we will be speaking with Dr. Jeffrey Weber. He is senior investigator of a phase two clinical trial for an mRNA melanoma vaccine. This vaccine has significantly reduced the recurrence of tumors in patients when combined with an immunotherapy drug. Hi, Dr. Weber, welcome to *On Medical Grounds*. Tell me about yourself.

Dr. Jeffrey Weber
Hi there. Well, I'm a medical oncologist. I'm also the deputy director at the Laura and Isaac Perlmutter Cancer Center here at NYU Langone Health in New York City. And I've been in the immunotherapy field, shall we say, for a while. It's been at least 30 years.

01:38
Dr. Jane Caldwell
Researchers have been chasing therapeutic cancer vaccines for years. The data from your phase two trial are all over the news because the efficacy of the melanoma mRNA vaccine against tumor regrowth looks promising. Could you share the concept behind this particular mRNA vaccine?

Dr. Jeffrey Weber
Yes, over I'd say the last decade, it's become clear to the basic immunologists in the tumor field that the substances recognized by immune cells that are associated with clinical benefit with drugs that work in melanoma and lung cancer, head and neck cancer, and other malignancies are neoantigens. Neoantigens are substances that we feel are produced by mutations or genetic changes present in tumors, not present in normal cells. And those are so-called SNVs, single nucleotide variants. So those are genetic changes that you find in the tumor. And remember, tumors are very genetically plastic. They're always changing. And your normal cells develop mutations, but not so many. And they don't usually threaten your life.

But you get a lot of mutations in tumors, and the bad news is they lead to uncontrolled growth and progression of the cancer. The good news is that they potentially could lead to unique antigens or substances that could be recognized by the immune system. And the trial in question that I was the principal investigator of was the first time this neoantigen approach was utilized in a randomized study where you actually had a control arm. So previously these neoantigen vaccines, whether they be RNA or peptides, proteins, DNA, were tested in early phase studies where you looked at the tolerability, the side effects, whether it could mount an immune response, and there were small numbers of patients, and there was no indication or no way to know whether it was clinically beneficial. The way you find out if it's clinically beneficial is you do a randomized study, and you have a control arm, which is pembrolizumab, which works in high-risk resected

melanoma that's surgically removed but at risk of relapse. And the experimental arm is you add the vaccine to the pembrolizumab. And that's why that study was done. And it takes advantage of all that knowledge of neoantigens. And the neoantigen strategy was a mRNA strategy where you could concatenate or put together in like a string of beads, the mRNA sequences that encode multiple neoantigens all in one vaccine.

04:14

Dr. Jane Caldwell

Fascinating. So how does the mRNA vaccine alert the patient's immune system and cause it to attack the tumor?

Dr. Jeffrey Weber

Well, it's done in two ways. There's a minor way and a major way. The most important aspect of the mRNA is it encodes all of these potential protein sequences that could be recognized by the immune system in a cancer patient. And it's personalized. The genetic changes in a tumor that aren't present in the normal cell are unique to each tumor. That's good news and that's bad news, I suppose. Now, the bad news is you can't have an off-the-shelf RNA vaccine for everyone, but it has to be personalized.

The good news is, if that works, it's very personalized. So, what happens is the RNA gets injected intramuscularly. It's a milligram, which is, that's a lot of RNA sequences. That's many millions. And the RNA is encapsulated to protect it from being degraded by the body's normal enzymes. And it gets into the muscle, and it finds its way to what we call antigen presenting cells. And those are cells that can show the immune system an antigen.

It uncoats, it gets into the cell, and in the cytoplasm of the cell, there are things called ribosomes. Those are little factories. We call them organelles. And those little organelles will bind the RNA, and it'll translate the RNA into pieces of protein. The pieces of protein find their way into another organelle called the endoplasmic reticulum. And there they get chopped up into little bits by what I think of as the garbage machine of the cell. It's essentially like a food processor. It sort of chops up the proteins into little bits and eventually most of them get discarded. But many of them will not get discarded and the little bits, which we call peptides, make their way in the endoplasmic reticulum onto the surface of something called MHC molecules and they get kicked out onto the surface of the cell where they can be recognized by the immune system. So, the RNA encodes the protein, the protein gets made in the cell, it gets chopped up into little bits, and the little bits are what are recognized on the surface of the cell by the immune system to generate an immune response and clear the tumor.

06:34

Dr. Jane Caldwell

Is this the first proof-of-concept trial supporting the potential clinical benefit of mRNA vaccines against tumors?

Dr. Jeffrey Weber

This is the first randomized trial that shows there is likely to be clinical benefit for adding the mRNA neoantigen vaccine to an established effective therapy, i.e., a PD-1 antibody like pembrolizumab, that was the one we used, which was compared to the active control arm of pembrolizumab alone. At the end of the day, you can do as many single-arm studies as you want. Proving or suggesting clinical benefit would

require the conduct of a phase two randomized trial. At the end of the day, the definitive evidence is you do the big phase three study, thousands of patients, and you compare the combination to the single agent pembrolizumab, and that's when you're absolutely unequivocally sure in a statistically significant way that the combo is better than the single agent.

07:38

Dr. Jane Caldwell

Let's talk a bit more about personalized medicine. These mRNA vaccines are created individually from mutations on a patient's tumor. Can you describe the laboratory process of mRNA vaccine creation?

Dr. Jeffrey Weber

So, it's a little complicated, although it's all sort of 2000s technology. It's not like something invented last year. You get a biopsy of the tumor before you start. We usually take a couple of core biopsies with a thick needle. You only need a couple of millimeters worth of tumor, like one millimeter cubed. It's a tiny amount. And that goes into a solution which generates the nucleic acids. And you do two types of sequencing of the tumor. You get a sample of blood with a regular blood draw to sequence the normal tissue, so the normal peripheral blood cells, and you compare the RNA sequence and the whole exome sequence, as we call it, of the tumor to the normal tissue, and you make sure the mutations or the genetic changes are present only in the tumor, not in the normal tissue. That's the definition of a neoantigen, by the way. And that process literally takes a couple of days. And then with a computer algorithm, you define what are the most important sequences that are mutated in the tumor, not present in the normal tissue. You take your 30, up to 34 best candidates, and you concatenate them into an RNA molecule. And synthesizing RNA takes like hours. It's old technology. And you take that long RNA molecule, which is hundreds of nucleotides long, and it folds itself into this encapsulated nanoparticle-encapsulated vaccine. That's the vaccine. And you do some QA/QC testing on the vaccine, and then you're ready to roll it by seven weeks.

09:28

Dr. Jane Caldwell

Are there any side effects to this vaccine?

Dr. Jeffrey Weber

As you can imagine, if you've had a COVID RNA vaccine, which I hope you have, I've had, oh my God, I've had six of them. I just had my most recent boost last week. There are definitely side effects to any RNA vaccine. The side effects of the current vaccine in the current trial are similar to what you'd see with a COVID RNA vaccine, but they're probably exaggerated because you're getting pembrolizumab at the same time. That's essentially an immune booster. And obviously [with a] COVID vaccine, you just get the vaccine. You don't get anything else. So, you know, patients have feverishness, shaking, chills, muscle aches, lethargy, a little bit of fatigue, a rash, pain at the injection site. That can last for up to 48 hours after the injection. 89% of the patients had what we call grade one, [grade] two side effects, which means they're not severe. They're not like life-threatening or even severely impact on quality of life. But, you know, 10 or 11 percent have what we call grade three side effects. You know, you might have a really high fever of 103. You might be bedbound for a day, just feel really crappy. To tell you the truth, after my last COVID vaccine last week, I felt pretty blah for a day. I mean, I had a low-grade fever, my arm ached, I couldn't exercise. So, you know, it's an exaggeration of the COVID vaccine effects. Is it tolerable in my view? Yes. Did any of the patients we treat have to stop because of vaccine side effects? No, but it, I suppose, could happen. All in all, there was

a moderate level of additional toxicity added by the vaccine to the pembrolizumab. And the serious side effects and the high-grade side effects were similar between the two arms.

11:19
Dr. Jane Caldwell
How is this vaccine similar or different to the mRNA vaccines used for COVID-19?

Dr. Jeffrey Weber
Well, again, remember the COVID vaccine is an off the shelf vaccine. It varies from year to year, depending on the mutations and the differences in the strains of the virus. But once you define the particular strain, like the one I got, I guess, had the standard strain plus Omicron sequences, it's off the shelf for everyone. Everybody gets the same vaccine. The difficulty with a cancer vaccine that immunizes you against neoantigens is everybody gets a different vaccine. It's utterly personalized. Even then, there's no reason why that, with current technology, why that won't be practical in many thousands of patients. It obviously was very practical in the current trial of 157 patients. Over time, as the technology gets better and better, I think it'll be even more practical. But yes, it'll take six, maybe take four to seven weeks to make the vaccine.

The good news is that's why you're treating resected patients. The likelihood you're going to progress in the first six to seven weeks if you have resected high-risk melanoma is pretty low, especially if you're getting an effective adjuvant therapy like pembrolizumab. So, the pembrolizumab holds things, prevents relapse, and then you come in with the vaccine to boost the effect of the pembrolizumab. Or I should say the pembrolizumab boosts the effect of the vaccine.

12:52
Dr. Jane Caldwell
Describe your 'bedside to bench to bedside' approach to clinical research.

Dr. Jeffrey Weber
Well, at our institution, I think we certainly are practitioners of innovative clinical trials based on science, much of which came from our own institution, where the basic scientists, the translational scientists, will develop concepts. People like me, and I'm primarily a clinical researcher and a translational researcher, people like me will peruse the data. We'll say, wow, that's like a great idea. I love that.

Or we'll read the literature and say, hmm, interesting. I think that's really impressive. And we'll try to devise a clinical trial, and that's what I do for a living, I write clinical trials, with correlative marker studies to try to determine whether the information that came out of a mouse would be something you can translate to a human being. And to do the studies to determine when it works, why it worked, and if it doesn't work, why didn't it work? And that's what I've basically been doing for a living for the past 30 years. And you then write grants to the NIH to support such studies, which can be an agonizing process, which takes literally many months to years. But at the end of the day, the government will send you money to understand these things. You'll spend the money wisely. You'll make incremental advances. And then you go back to the bedside. You'll go from the bench to the bedside, do the trial, do the preclinical work at the bench to try to understand, like I said, if it works, why did it work? If it didn't work, why didn't it work? And then go back and design a new trial based on that information.

14:34
Dr. Jane Caldwell
How does a cancer patient get involved in a clinical trial?

Dr. Jeffrey Weber
Well, most of our patients who go on trials are already in our clinics, and we have a very busy surgical group in melanoma, so most of the patients we see come from the surgeons. And the surgeons will operate on them, and for example, for this trial, virtually everyone who went on the trial had surgery at our institution, and they were then sent to us by our surgical colleagues to do our consultations as the medical oncologists and decide what further therapy, if any, was indicated, and we would offer a menu of options including this trial to them. And the patients would then look at us and say, well, you gave me three options, what would you do? And usually I would say, well, if I had the possibility of going on a randomized trial where at the worst, I would get the same old standard therapy I'd get anyway, and I had a two thirds chance of getting a very promising neoantigen vaccine, I'd jump at the chance to go on the trial.

And I always point out, I'm biased, I'm the principal investigator of the trial, but nonetheless, if you were my brother, sister, mother, father, whatever, I would tell you to do it. So, but most, and sometimes patients will come to us from other institutions. For example, later this morning, I'm seeing a lady from Pennsylvania, who's looking for a trial, and people go online, and they see what the options are. Let's say their institutions don't have a trial, they might look to us. Sometimes my colleagues at other institutions around New York will call and say, hey, you know, do you have a trial for this type of patient? And if the answer is yes, they'll say, well, I'm gonna send you my patient, Mr. or Mrs. So-and-so. So that's how they come to us.

16:23
Dr. Jane Caldwell
Well, your argument for being in a trial is very persuasive. You know, we're always talking about the cure for cancer. What is the research definition of a cure? Is it 100% of patients with no recurrence or is it something different or less?

Dr. Jeffrey Weber
Well, I'm not sure that there's a research definition of cure. Patients who ask me that question, I tell them, if you die at the age of 99 with your boots on and you have an autopsy showing no evidence of melanoma, if it's a melanoma patient, I think that's a pretty good definition of cure. In melanoma, the likelihood of relapse is exponential, and it's much higher for the first two years than it drops for the next couple of years. The problem with melanoma is you could relapse 20 years later. But what I tell patients is if you get to year 10, first if you get to year six, it's time to have a party, celebrate. If you get to year 10, I think you can safely assume you're out of the woods and you're probably never gonna relapse, with the caveat that every once in a rare while we'll see someone relapse 20 years later. But cure means you never relapse and you go a certain amount of time, and it varies by tumor. Breast cancer, that might be five or six years.... In melanoma, it might be 10 years. With other tumors, it will vary, but if you don't ever relapse, you're not gonna die of cancer. Because if you don't relapse, there's no cancer, by definition.

17:52
Dr. Jane Caldwell
Preventing the regrowth of the tumor has been called a clinically meaningful endpoint by one of your colleagues. Are there other clinically meaningful endpoints in cancer therapies?

Dr. Jeffrey Weber
Well, the ultimate endpoint in cancer is survival. I mean, if I were a patient, and as I think I may have mentioned, I am, I have been a cancer patient, I'd want to know, am I going to live or am I not going to live? I think survival is the ultimate endpoint. Anything else is a surrogate, a substitute for that. Recurrence-free survival, distant metastasis-free survival, in metastatic disease, response or shrinkage, progression free survival, those are all meaningful endpoints, but they're all surrogates. At the end of the day, you want to know, am I going to be alive or am I not going to be alive at year five or year 10 or whatever? And that's, like I said, to the FDA and to me, that's the ultimate end point.

18:49
Dr. Jane Caldwell
So, what's next for mRNA antitumor vaccines?

Dr. Jeffrey Weber
Well, there will be a large definitive registration phase three study that Merck will conduct, because Merck and Moderna co-developed the current vaccine in the trial that I was the PI of. And they're gonna do a large randomized thousand or so patient study with resected high-risk patients who will get in the same way either the combination of the mRNA vaccine with pembrolizumab or pembrolizumab.

And that study will, I think it'll fill up very quickly. It'll accrue over a year. It'll start this summer. By June of 2024, I hope it'll be done. And a year, year and a half after that, I think we'll have the answer. Because enough events, meaning a recurrence, will have occurred between the two arms to see what the difference is.

19:38
Dr. Jane Caldwell
That's exciting. Now you mentioned a personal connection with cancer. Could you share a little bit with us?

Dr. Jeffrey Weber
Well, without giving specific details, I am also a cancer survivor, and at some point, I will also get a cancer vaccine. So having had a significant malignancy, it definitely changes your opinion about how we subject our patients to therapies that can cause side effects. Having seen some of those side effects personally, I think it definitely gives you some pause and some sympathy for how people react to various treatments, which for most cancers are chemotherapies, but of course can be immunotherapies.

20:22
Dr. Jane Caldwell
As an oncologist and professional healer who sees cancer on a daily basis, what keeps you up at night?

Dr. Jeffrey Weber
Fear that I missed something or that I mismanaged a potential side effect. Anybody in my view in the business who's any good is going to be somewhat paranoid about did they do their job right, did they do it completely, did you see Mr. So-and-so and get all the tests or Mrs. So-and-so and get all the tests that you needed. And then when patients get really bad side effects from immunotherapy, particularly, which is what we use mostly in melanoma.

For example, there was once a patient, this is a long time ago, 20 years ago, when I was in Los Angeles at the University of Southern California. This was a patient who had the worst case of colitis I've ever seen. It was a guy who had toxic mega colon, which means his colon was dilated, like it was about to blow up. And I was convinced he was going to die. And every day, I would go to sleep thinking, Jesus, am I going to wake up in the morning, call in and find out that the guy is intubated and he's about to die. The guy amazingly made it through a week in the ICU, never got intubated. He had a surgical procedure to decompress his bowel. He got put on big time steroids, it resolved his colitis. He never got treated again with immunotherapy. He was cured of his disease because 15 years later he sent me a postcard saying that he was retiring from his job. He was a high-level executive at a tech firm. And I didn't believe it because I had left Los Angeles, that was the last I heard of him. I didn't know what happened to him. So, he said, yeah, I'm doing well. I looked you up, I see you're now in New York, blah, blah, blah, blah, blah. Hope you're doing well. And I wrote back to him, and I said, tell me something, if you had to do it again, would you do it again the same way? He said, yeah. So that blew me away. On the other hand, he was cured of melanoma. It was 15 years later, and he was free of disease. So that was the sort of story, that was the kind of case that kept me up at night. No question.

22:28

Dr. Jane Caldwell

Well, great story. Dr. Weber, we admire and applaud your team's innovative research with melanoma therapies. I hope your phase three trials continue to show mRNA vaccine efficacy. Thank you so much for taking time from your busy schedule to speak with us.

Dr. Jeffrey Weber

Thank you, thank you for having me.

Dr. Jane Caldwell

And thank you for listening to the *On Medical Grounds* podcast. We know your time is valuable.

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