Patient Education for Melanoma Skin Cancer

Immunotherapy in Treatment of Melanoma

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TRANSCRIPT

So I wanted to start with a discussion on immune therapy. Your doctor might tell you that they recommend immunotherapy for your treatment. And if we think about immunotherapy, I think it's important to understand that in all of the historical treatments of cancer — and melanoma is a type of cancer because it's related to cells that are dividing abnormally — what happens is in normal cell division, a cell goes from one to two, and from two to four, and if there's a damaged cell, it undergoes something called apoptosis; apoptosis means it self-destructs. So if it makes a bad version of itself or a bad copy of itself, it will just destroy itself and disappear, and that bad copy goes away. It was like a mistake, you hide the mistake and it goes away and it never ever happened.

But what happens in melanoma and other cancers is that cancer cells keep dividing, even though they are mistaken. So if the cell divides and it shouldn't have divided; in theory, it should just go away, but in cancer, those cells continuously divide and divide, making many abnormal copies of themselves. And we don't want that growth to happen because that's called a tumor or an abnormal growth. And in the case of melanoma, there are different signals that cause these cells to grow and divide and keep growing when they shouldn't be growing and dividing. So, the idea of immune therapy is so that the body's own immune system can police this type of abnormal growth and hopefully destroy the cancer cells.

And this theory originated in the late 1800s by this gentleman, Dr. William Coley. He was a bone and soft tissue surgeon that dealt with cancer patients at the turn of the century. And here's a picture of him from actually a Christmas party in 1892 of all things. And he was noticing that when he treated patients like this gentleman, around the turn of the century, with a big tumor under his right ear, what would happen after surgery is that some of these patients would have infections because they didn't believe in antibiotics in the same way that we give antibiotics now to treat infections. And when these patients had bacterial infections, postoperatively, their immune system would go into overdrive, and that would result in them having, in some context, a lot of fevers and chills and being unwell because it’s the infection they were dealing with. But very interestingly, some of their tumors spontaneously went away. So, this Dr. William Coley thought, “Well, that's really interesting. If we can find a way to turn on immune response.”

And historically, that was only done by these bacterial infections, now we have drugs that know how to do this. But historically, “If we can find a way to turn on immune response and help cancer progress, then then we're really on to something.” And that's the principle of immunotherapy. This is a cartoon, also, of what is seen with a certain kind of electron microscope. And you can see a cancer cell, this red cell in the middle, kind of like a meatball. And that certain cell of the immune system called a cytotoxic T cell, coming in extending some tentacles and trying to destroy the cancer cell. So all immune therapy does is try to enhance everyone's immune system that fights off bacteria and viruses, and the intent is to also fight off cancer cells.

So, how does that work? How does an immune therapy approach help T cells to go kill a cancer cell and kill melanoma? This is what it looks like under the microscope. At the top is a tumor, and at the bottom, all these tiny little purple dots are little T cells or lymphocytes that go in — and think about them as an Army — rushing forward from the bottom to the top of the screen, percolating amongst the tumor cells and trying to kill them like I showed you in that last example. That's what we want to happen. We want our own body's immune system as an army to come and seek and destroy melanoma. And there are a lot of strategies that try to do that.

But why doesn't it work all the time? Why isn't our immune system already trying to kill the cancer cells? Why does melanoma even exist in our bodies in the first place? And the purpose of that is, think about this as a melanoma. Melanoma comes from normal melanocytes like I talked about in the beginning when it showed that cartoon of how that works. And these normal melanocytes are part of our normal body tissue. So sometimes tumors are hard for the body to see immunologically. The immune system is looking for bacteria and viruses, it's not sometimes looking for normal melanocytes that have gone rogue to become melanoma. So here's the tumor, it's hiding out in normal healthy tissue.

So, what we want to do with our treatments in different combinations is to make the tumor look different. So, these are the antigens that a tumor may be expressing on its surface to make it look different to the immune response. And when it looks different to the immune response, that's when the immune response can recognize it as a foreign material, like a bacteria or like a virus that needs to be destroyed. And then the immune cells come into the tumor microenvironment, those little purple dots like I showed you on the last slide, or at least a lot of substances to seek and destroy the tumor cells.

Now, there are a lot of different ways that we can enhance this normal anti-tumor immune response, and one of them is through drugs that make the T cells work stronger. How does that work? Well, T cells are normally kept perfectly in a luke-warm situation. So, if you're thinking about heating up the bath water for a kid to go in the bath, you don't want it too cold, you don't want too hot; you want it just the right temperature. So, T cells can be too hot, and that means the immune system is too on, and that means that you have an autoimmune disease. Or they can be too cold, which means that you may be susceptible to infections and additional cancers. So these T cells are kept in this perfect equilibrium or in a lukewarm temperature by go signals on the T cell and by stop signals on the T cell.

And if you stop the T cell by enhancing the activity of these stop signals, that's a way to turn down the volume. If you want to turn up the volume of the T cells, different drugs stimulate these go signals. So, a lot of the immune therapy strategies that were given to patients with cancer block these inhibiting molecules and thereby make the T cell work more strongly. So think about it as taking the brake off of your car, you're going to drive a lot more quickly because you can't stop. So we want the T cells to fight the melanoma harder. And the drugs that are FDA approved for melanoma including pembrolizumab, nivolumab, ipilimumab, and I'll talk about relatlimab later — these drugs act by blocking these stop signals on a T cell. And by taking down the stop sign, taking off the brake, blocking the negative signal on the T cells — that makes these T cells actually work harder.

There's a new drug that was just approved by the FDA in 2022, called the relatlimab. And this is combined with a drug called nivolumab. Relatlimab blocks another stop signal on T cells called LAG-3. You can see LAG-3 at the bottom-right of this cartoon. And I wanted to mention, incorporating relatlimab plus nivolumab was shown to be better than nivolumab alone.

So, we have now three different places on a T cell where we can enhance the efficacy of the T cell response against melanoma tumors. It can shrink melanoma in Stage Four setting, help people live longer. And in the Stage Three setting, it can help prevent melanomas from recurring. We don't yet know in the Stage Three setting of people that have had surgically resected Stage Three melanoma if immune therapy helps people live longer, but it does help prevent their melanomas from coming back.