Welcome to CME on ReachMD. This segment, entitled Fundamentals of Cancer Immunotherapy is provided by Prova Education and the Roswell Park Cancer Institute as well as through the generous support of BlueCross BlueShield of Western New York.

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Dr. Chatta:

Hi, I'm Gurkamal Chatta. I'm the Chief of Genitourinary Oncology at Roswell Park Cancer Institute, and today we're going to talk about the Fundamentals of Cancer Immunotherapy.

So, here are my disclosures. So, I was a consultant to Bristol Meyers Squibb, and I'm also on the Speaker's Bureau for Immuno-oncology.

So, the learning objectives for today are basically going over the role of immuno-surveillance, and its role in cancer control. Then briefly discuss what we mean by what a productive immune response is, then go on to how the cancer responds to the immune system and what the immune system does to
the cancer, and then, finally, we'll touch upon some important new advances in human cancer immunotherapy.

So, this is actually a classic slide from Weinberg and Hanahan, who are two well-known cell biologists who have been working upon what the hallmarks of cancer are, in other words, how does cancer grow, sustain itself and spread? And they came out with their first paper in the year 2000, but as you'll notice here, in 2011 they revised the hallmarks and they recognized an important role for the immune system in helping us both control and prevent cancer.

So, essentially, when you kind of look at this cartoon, whether or not cancer is controlled or even the first place whether it develops depends on a balance between immune protection and immune invasion. So if the immune system gains the upper hand, we don't develop cancer or at least control it even if you do develop it; whereas, on the other hand, if the cancer is smarter, it can invade the immune system and spread and essentially kill us. So, this again kind of depicts that immune protection and immune invasion.

This is another slide which again speaks to the importance of the immune system and its role in cancer, and as you can see, if somebody's immunosuppressed -- and this is data from a number of people who have undergone organ transplantation and have been on immunosuppression -- almost every cancer goes up anywhere from 2-fold to 20-fold. Now, traditionally, what we recognize is things like melanoma, kidney cancer and lymphoma. They are the ones that happen most often when we are immunosuppressed, but again, as you can see, virtually, any cancer the incidence goes up if the immune system is suppressed.

Here is another slide which speaks to the importance of the immune system in cancer, and what we know is, in cancers where the immune system successfully controls it or prevents it, you'll have T cells, which are one kind of immune cells which go into the cancer. Now, this is from patients with colorectal cancer, but essentially, this study has been replicated in many other different cancers.

So, what are the key components or the important components in the immune response? Now, clearly, there are many, many different molecules and cells, but some of the important ones are the antigens. So, these are the proteins which constitute a cancer or constitute a cell, and they have to be released. Then they have to be recognized and processed by antigen-presenting cells. And next, the antigen presenting cells will activate either T cells or B cells. So, once again, I mean, this is a very simplistic depiction of all this, but these are the key components, and we'll go into these a little more in a second.

I think if you were going to read one paper to kind of get a grasp of cancer immunity, the one I'd recommend is by Chen and Mellman which came out in *Immunity* in 2013, and really what this does is
it kind of walks us through this whole process, which is depicted here.

Now, the good thing about this is it's broken up into 7 different steps. So, in step 1 the cancer first has to release the antigens or the proteins that make it up. Once they are released, they are recognized by the antigen-processing cell or dendritic cells. Once it's recognized, once the cancer is recognized or part of it is recognized, the dendritic cell goes to the local lymph nodes where it activates the T cells, which is one kind of immune cell we talked about. Once the T cell is educated, it expands, and grows in number, and through the blood vessels or circulation goes to where it needs to go. Once it gets to the site of the tumor, it has to get into the tumor, and once it gets into the tumor, it actually has to kill it. So, again, there are 7 different steps, and as you see here, the stuff in green and stuff in red. So, these are factors which help the process, and in red are the factors which dampen it down or inhibit it. So, again, it's that same seesaw. There's a balance between the green stuff and the red stuff. And at every given step, there are factors which either facilitate the whole process or inhibit the whole process. So, as you can see, the whole thing is incredibly complicated, and what researchers have been working on is basically facilitating the green stuff and dampening down the red stuff. And there are literally thousands of factors which are important, and it's really taken all these 20, 30, 40 years to figure out where, when you perturb the system, you actually make an impact. And, clearly, we are nowhere near the end of all this. We are still if the beginning stages. And to cut a long story short, what's really turned out is if you block the red stuff -- so in other words, if you remove the brakes on the immune system -- you're actually able to treat tumors much better, as opposed to enhancing the green stuff. And, again, this has been through experimentation done in the last 20 to 30 years.

So, what I want to draw your attention to is 2 molecules. One is CTLA4 and the other one is PD-1. Now, both of these are, for lack of a better word, immune brakes on the T cell, and if you remove these brakes, you can actually activate the immune system, and that's what most of the recent excitement is about and that's where most of the advances have happened.

So, just like a brief summary then: What are the features of an effective immune response? You have to have a target. Once you recognize the target, the immune cell has to go to the area of interest or traffic there. Once it goes there, it has to kill the cell. And then, also, what you're hoping is that the whole process spreads, and then finally, you have a memory for that. So, probably, this is best depicted in the next slide.

So, this is a normal immune response to smallpox. Now, all of us know a single vaccine shot can really confer immunity for the rest of one's life. So, even if one is, even if you look at 50- to 75-year-olds, 60% of people have a good immunity to smallpox. So, really, the goal is if in cancer we could do the same thing, if you could elicit a strong immune response against a cancer and, more importantly, have
memory for that, then we should be able to cure it. Now, we are nowhere near there, but we are slowly making a progress in that direction. And I think the main reason to put this slide up is that this is what we actually want to aim for for some time in the future.

So, the next slide just basically encapsulates the fall and rise of immunotherapy through the ages, and as you will see, the hopeful phase has really been since the late '90s. So, in 2010 we had the first vaccine approved for the treatment of cancer, and that was for prostate cancer. And then in the last 3, 4 years, we have 2 checkpoint inhibitors that have been approved for melanoma, for lung cancer and for kidney cancer. And these checkpoint inhibitors are the same ones that I talked about initially, that is, removing the brakes on the immune system, i.e. blocking CTLA4 and blocking PD-1. So, you know, at the risk of, again, repeating myself, but I do think it's important, so there is CTLA4 once again and PD-1 once again, and these are the 2 important brakes on the immune system, which if you remove them, you can actually activate the immune system to fight the cancer. So, once again, CTLA4 and PD-1, these are expressed on the T cells. They act sequentially. And really now people are looking at combinations of blocking both this and this, that is the CTLA4 and PD-1, and seeing how effective the whole system is. And once again, the cancers that these checkpoint inhibitors are approved for are lung cancer, melanoma and kidney cancer, melanoma having been the first one, and they have been tested in a host of other cancers, and we are hopeful that they will get approved for the treatment of other cancers as well depending on what the studies show.

And this cartoon again is really just to put things in context. CTLA4 is just one small thing here, and PD-1, again, is one small thing here amongst many, many other factors. So, again, the whole intent of the slide is to show that the system is much more complicated than we realize. What I talked about probably works in about 30 to 40% of cancer patients, so clearly, there's a lot of room to improve and do much, much better.

I guess the other unique thing about immunotherapy or how the immune system works is it's very different from your radiation and chemotherapy. And this slide is from a patient with melanoma, and what you see is this is where the treatment was started, which is day 0, and it only cleared after a year and a half -- that's 503 days. In fact, in the first few weeks and months, the tumor actually grew, and it's only after that that it started subsiding. So I think one very, very important thing to keep in mind with the immunotherapies is how you gauge response is different. So the immune system doesn't work overnight. In fact, it takes months, can even take a year. So one of the bigger challenges we have is if you treat somebody and you see them 6 weeks later and, in fact, the tumor has grown, you actually really need to be sure that it's true progression and not pseudoprogression. Now, it doesn't happen to everybody, but it does happen in about 20% of patients, that actually the tumor grows, and if you were to biopsy one of these lesions, what you would find is there are a lot of immune cells in there. So, it's
not like the tumor has grown, but the immune cells take time to work. They go in there. The lesion seemingly grows. And it's only later on that it starts shrinking. So, before you throw the baby out with the bath water, you just have to make sure that things have really progressed and not pseudoprogressed. So, once again, to emphasize, it's not something that happens in all, in everybody. I mean, very often when a tumor has seemingly grown, it's true progression and not pseudoprogression. It's just important to be aware that there is something known as pseudoprogression as well.

So, kind of moving on towards the end, when we look at the future of cancer immunotherapy, we talked about checkpoint blockade, and that's primarily what we talked about so far, and clearly, there's a lot more that still needs to be done to improve that. What's also crucial is that we understand better where to target a particular cancer. Most of cancer studies so far with immunotherapy have been done in advanced stage. Clearly, if you think about the way the immune system works, i.e. it prevents infections or prevents cancers, the sooner we use it, the better off we are, so clearly, targeting disease subsets as we go into the future is going to be important.

And the other things which have generated a lot of excitement are the so-called chimeric antigen receptor T cells, or CARs. I mean, that's the acronym for that, C-A-R, CARs. And the reason they have generated excitement is here you can get a T cell, educate it to specifically recognize a tumor, then expand the T cells and then give it back to people. Now, it sounds simple, but there's a lot of genetic engineering involved in that. It's nowhere near primetime, but at least for some leukemias, it's beginning to show impact. In fact, these are people with leukemia who failed bone marrow transplants and they are being treated with CARs. At least we've seen some initial success.

So, the purpose of this slide is just to confuse. It's no more than that. It specifically talks about the CARs. And what you'll see is the recognition part of the CAR has not changed. That is that the stuff in violet. But then if you look at the internal part which makes the CARs go, that has been engineered. So, this was the first generation, these are the second generation, and those are the third generation. And, once again, this article was in the New England Journal, and I just put it down there as a good reference, because again, I think this is probably going to be a part of our armamentarium in cancer immunotherapy in the future.

So, finally, to summarize, the immune system place an exceedingly important role in controlling cancer. Immunotherapies boost the ability of the immune system to fight cancer. Long-term survival has been shown with several immunotherapies. Now response criteria and how you gauge immunotherapy works are unique, and one needs to be cognizant of those. And the hope is that efficacy may be improved when we start using immunotherapy early on in the course of the disease.
Thank you for your attention and thank you for listening to me. Once again, my name is Gurkamal Chatta, and if you have any further questions, please feel free to contact me through roswellpark.org.

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