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# Advances in the Treatment of Glioblastoma Multiforme: Is There a Role for Immune Checkpoint Inhibitors?

Narrator:
Welcome to CME on ReachMD. This segment, *Advances in the Treatment of Glioblastoma Multiform, or GBM: Is There a Role for Immune Checkpoint Inhibitors?* is jointly sponsored by the Johns Hopkins University School of Medicine and Advanced Studies in Medicine and supported by an educational grant from Bristol-Myers Squibb. The target audience for this educational activity includes physicians and other healthcare professionals who manage patients with GBM.

Your host is Brian McDonough, and our guest today is Dr. Michael Lim. Dr. Lim is the Associate Professor of Neurosurgery, Oncology, Radiation Oncology and the Institute of Nanobiotechnology. Dr. Lim is also the Director of the Brain Tumor Immunotherapy Program and Director of the Metastatic

Brain Tumor Center at Johns Hopkins University School of Medicine.

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Dr. McDonough:
Despite significant progress in the treatment for glioblastoma multiforme, or GBM, patient outcomes have failed to see a drastic improvement. Recently, immune checkpoint inhibitors have shown promise in treating GBM in cases where conventional treatment options have failed. The rapid progression of GBM necessitates timely and well-informed decisions made on the part of the clinician. Thus, as research emerges on novel treatments that may fulfill a significant unmet need among patients, clinicians need to be knowledgeable of the growing evidence regarding the immune system in GBM and the most up-to-date clinical data regarding immune checkpoint inhibitors as treatment options.

I am your host, Dr. Brian McDonough, and with me today is Dr. Michael Lim, Associate Professor of Neurosurgery, Oncology, Radiation Oncology. Dr. Lim is the Director of the Brain Tumor Immunotherapy Program and Director of the Metastatic Brain Tumor Center at Johns Hopkins University School of Medicine.

First of all, it's an honor to have you with me, and thank you so much for joining us, Dr. Lim.

Dr. Lim:
Thank you, Brian. It's a pleasure to be here.

Dr. McDonough:
What is the basis for looking at immunotherapy for GBM?

Dr. Lim:
As you mentioned earlier, glioblastomas are probably one of the most aggressive types of tumors that we know of, and, as you had mentioned earlier, despite some of the latest therapies including surgery, chemotherapy and radiation, we have made a modest improvement in terms of survival for our patients. And so, if we think about glioblastomas, I think one of the important things to think about is the fact that it's not really a local disease, and because it's not a local disease and because it's so hard to treat with conventional therapies, novel therapies or novel approaches are needed. And if you think about a different type of approach or think about novel approaches, you would want that approach to be able to provide surveillance to allow for eradication of the tumor cells as they recur and allow for a more global response against the tumor. Glioblastomas often are not just contained within the enhancing region such as you see on an MRI. So immunotherapy fits that bill in the sense that it allows for immune cells to provide surveillance and to treat a tumor that's more global than localized.

Dr. McDonough:
Isn't the brain immunoprivileged to hinder immunotherapy approaches, and are brain tumors different from other tumor types?

Dr. Lim:
If we talk about the brain and brain tumors, I think people think about the brain as an immunoprivileged site, as you had mentioned. That really came from work that was published in the 1940s by Dr. Medawar, and what he did was he took skin allograft cells and essentially implanted them into the brain, and then he came back and opened the brains up of these animals and looked at them and found that these cells had engrafted and were still alive, whereas if you implanted those cells elsewhere in the body, they were essentially rejected by the immune system of the animal. So, based on his observations, he concluded that the brain was an immunoprivileged site.

In addition, other people believe that other reasons for this immunoprivileged phenomenon is the fact that there is this tight blood-brain barrier and that the barrier itself could limit the trafficking of immune cells in and out of the brain. Also, many people believe that there was an absence of lymphatic in the brain, and that again contributed to this immunoprivileged site. However, today we know that the brain, or just the central nervous system itself, is still very capable of producing an immune response. You know, we looked at patients who have, for example, an encephalitis or a brain abscess. We observed very, very vigorous immune responses. In addition, there was a paper that was published in *Nature* recently that showed very nicely that there are actually lymphatics in the brain. These lymphatics drain into the deep cervical lymph nodes. If we look at the tumors that arise in the brain, including tumors like glioblastoma, we do see tumor-infiltrating lymphocytes, which again suggest that the immune system is providing a surveillance function and probably has recognized specific antigen on the tumor.

Dr. McDonough:
We were talking about also how the brain tumors might be different than other tumor types.

Dr. Lim:
Right. So, in terms of how brain tumors differ from tumors in different parts of the body, one of the experiments that we did in my lab -- Chris Jackson was my post doc -- he specifically asked that question about whether or not having a tumor in the brain changes the immune system differently, could negatively or positively affect the immune system compared to having that same tumor in the periphery. And so what he did was he basically took two sets of mice, and we took a set of cells called B16 OVA, which is a melanoma cell line that expresses a very unique peptide called OVA, and he implanted these tumors into the brain in the first set of mice, and he implanted the second set of cells into the back or the flank in the second set of mice, and then what he did was he did an adoptive

transfer of T cells. And with this system there is actually genetically bred mice that have T cells that specifically recognize OVA, so you have an antigen-specific T cell, and you can harvest these T cells and inject them or adoptively transfer them into the mice. And so when he did that, he looked at the T cells both in the mice with the brain tumors and in the mice with the flank and noticed that when the mice had brain tumors, these T cells were actively deleted, and the remaining T cells that were viable were actually inactivated. They could not secrete this cytokine called interferon gamma, which is really an indicator of the activation status of T cells. In addition, those T cells could not divide. However, if you looked at those T cells in the animals that had the tumors in the flank, those T cells had the ability to divide and were actually active in performing some anti-tumor effect or killing. So, from his study he showed that, in fact, if you have a tumor in the brain, you could actually have an active deletion of T cells, and those T cells had a decreased ability to divide and they were inactive. And we tried to look at the mechanism behind this, and we found that there is probably multiple factors that explain this, but TGF beta, which is another cytokine, seems to be mediating this suppression.

There was a very nice paper that was published by Dr. Bloch and Dr. Parsa out of Northwestern where they looked at patients with glioblastoma, and they specifically looked at the blood, the peripheral blood of these patients, and they sorted out the macrophages. When they phenotyped them, these macrophages were expressing a ligand called PD-L1, and this PD-L1 really indicates that these macrophages are more immunosuppressive. And what they did was they cocultured these macrophages with the patient's T cells, and these macrophages actually caused these T cells to be inactivated. Some of these T cells underwent apoptosis. So, there is actually evidence in both humans and animal that having a tumor simply in the brain can cause not just immunosuppression in the local microenvironment but globally throughout the body, and that's something we think that is more unique to the brain than tumors that arise elsewhere in the body.

Dr. McDonough:
I wanted to switch gears for a second if I could and talk about checkpoint inhibitors. What are they, and do they have a role with brain tumors?

Dr. Lim:
Checkpoint inhibitors have been a major revolution in terms of cancer care, and checkpoint inhibitors are referring to a class of molecules that are involved in activating or inactivating T cells. So, it turns out that when a T cell with its receptor encounters its specific antigen that's expressed either on the antigen-presenting cells or on the tumor cells -- and again, it's on the MHC complex -- these T cells then dock and bind to that MHC. They then need a second signal, and the second signal can either turn the T cells on to do their effector function or turn the T cells off, and this second set of interactions are called the checkpoint molecules or the checkpoint inhibitors. These checkpoint molecule interactions

are very important because it prevents autoimmunity in our own body. But it turns out that tumor cells have figured out that these checkpoint molecules are very powerful in helping them evade the immune system. So, when people began using these checkpoint inhibitors in cancer, they noticed very profound effects. Dr. Hodi in 2010 was one of the first people to publish with a Phase III trial that ipilimumab, which is an anti-CTLA4 drug, that when patients were given this anti-CTLA4 -- and again, these are patients with metastatic melanoma -- he noticed that about 20 to 30% of these patients had a durable response. And from that point on, a few years later Dr. Topalian published a paper in the *New England Journal* looking at multiple tumor types using another type of checkpoint molecule called anti-PD-1, and they found 20 to 30% of patients with melanoma, lung cancer and kidney cancer were again responding to this tumor, and there were dramatic regressions of tumors when these patients were treated with anti-PD-1.

As a result, we're living in some unprecedented times. In the past few years, the FDA has approved the use of anti-CTLA4 and anti-PD-1 for multiple cancer types -- melanoma, lung cancer, kidney cancer, Hodgkin's lymphoma and bladder cancer, and I think recently head and neck cancer -- so obviously, there's a lot of excitement for checkpoint inhibitors with many different tumor types, and we think it's particularly relevant for glioblastoma. Now, we don't have any data yet, but we hope to have data on glioblastoma this upcoming year.

When we look at glioblastomas, one of the most logical things to ask, first of all, is to ask if glioblastomas do express some of these checkpoint molecules? Dr. Heimberger and Dr. Preusserin separate studies have shown that the ligand for PD-1, which is called PD-L1, is expressed on glioblastomas, and they seem to be more expressed on gliomas, but they seem to be more highly expressed on glioblastoma. In addition, there's preclinical data that suggests that this could be an effective approach for glioblastoma. Dr. Fecci published a very nice paper in *CCR* in 2007 which showed that when you gave anti-CTLA4 to an animal with a glioma, they were able to improve survival. And what was interesting about that study was that when they gave anti-CTLA4, they noticed that the T cell function was restored. It wasn't increased but restored, because when they animals have tumors, their T cells are actually suppressed. Xiang Zhang, when she was a post doc in my laboratory, also showed that PD-1 could improve survival in animals with glioblastoma, and there have been subsequent studies that have confirmed this.

So, as a result there are now many ongoing trials looking at checkpoint inhibitors for gliomas, and one of the larger studies that we hope to get some information from this year is the CheckMate 143 study run by Bristol-Myers Squibb, and they are looking at giving anti-PD-1 or anti-PD-1 and anti-CTLA4 to patients with a first-time recurrent glioblastoma. The accrual has been completed, and we are awaiting the results. There are also some other studies that are looking at anti-PD-L1 antibodies.

Dr. McDonough:
If you are just tuning in, you are listening to CME on ReachMD. I am your host, Dr. Brian McDonough, and I am speaking with Dr. Michael Lim.

When we talk about immunotherapy, I'm always curious about the near future. There might be some indications or immediate uses for immunotherapy. Maybe you can discuss that a little bit.

Dr. Lim:
As immunotherapy is becoming more common therapy -- we haven't figured that out for glioblastoma -- but we in neurooncology are taking care of a lot of patients with brain metastases, for example. I think that we have to learn a whole new set of skills in taking care of patients who are undergoing immunotherapy. I think one of the most important issues that we have to understand are the toxicities associated with these immunotherapies. As I talked about a little bit earlier, the checkpoint molecules are there to prevent autoimmunity, but autoimmunity is a toxicity that has undergone these therapies. For example, colitis is a very common side effect of patients, and if we encounter a patient that's having diarrhea, our traditional thinking is to send him off for something like a C. diff workup, but I think it's very important that we consider colitis as part of the differential in our patients, and if so, it's important that we have good relationships with our colleagues in other specialties, such as GI, so that they know how to recognize patients with colitis. And the same goes for other side effects such as pneumonitis. Pneumonitis is a life-threatening complication if it's not recognized earlier, and that's a little bit more common with PD-1. And with some of these combination therapies, myocarditis is recently reported. For the clinicians it's important that we again learn to recognize and learn how to manage these patients who present with these toxicities.

Dr. McDonough:
That's really interesting, because what you're trying to do is also, I guess, in a way, educate the clinicians that are out there as to some of the new approaches and what's going on at least in the short term as well.

Dr. Lim:
Oh, absolutely, because it's a whole new way of thinking. We are not just turning the immune system on against the tumor but globally turning the immune system on in the patient.

Dr. McDonough:

Now, we talked a little bit about the short-term effects. What do you see about the future of brain tumor immunotherapy as we go forward and we learn more and more?

Dr. Lim:

As these trials unfold, what we've been learning with the different cancer types, particularly with checkpoint inhibitors, is that we find that some tumors are very responsive. And there's a term that's being coined called “hot tumors.” For example, melanoma is considered a “hot tumor” that responds to these checkpoint inhibitors. But there are certain tumors that don't respond to checkpoint inhibitors like prostate cancer and pancreatic cancer. One of the things that we have to figure out for glioblastoma is where it falls on the spectrum. Is it going to be a “hot” or is it going to be a “cold tumor”? But even with these “hot tumors,” as I alluded to earlier, only 20 to 30% of these patients are responding, so we have room for improvement. And I think one of the more immediate steps is to figure out combination therapies to try to improve the efficacy with the “hot tumors” and make the “cold tumors” more responsive. And some of the combination approaches that are being looked at are things such as combining checkpoint inhibitors, different checkpoint inhibitors, not just PD-1 and CTLA4, for example. The Adult Brain Tumor Consortium, we're running a combination of anti-LAG-3 and anti-PD-1 or anti-CD137 and anti-PD-1.

Another approach is to combine different modalities. For example, using focused radiation or stereotactic radiation seems to work with checkpoint inhibitors in a synergistic fashion. The thinking is that the radiation kind of creates kindling to generate a systemic response. Another modality is considering chemotherapy. One of the things that we have been looking at in our laboratory is using potentially local chemotherapy rather than systemic chemotherapy. Having local chemotherapy could again act as a kindler to cause a more systemic response.

Another thing that I think is going to be important to understand is to try to figure out which tumors respond and which ones don't. Biomarkers are going to be critical in this. Some researchers have found in melanoma that if the tumors express PD-L1, that they are likely to be a responder, and if they don't, they will not respond. Other examples is actually from studying lung cancer. They found that smokers generally respond better than nonsmokers, and it turns out that smokers just have a lot more mutations and there's probably a lot more antigen. And even things such as the microbiome, which is our gut flora, it turns out what you eat can actually determine the bacterial population in our flora, and if you have certain types of bacteria, you become more responsive to immunotherapy.

These are all external factors, as well as biomarkers, that can help really determine who could respond. And again, that would also help us minimize toxicity for patients who won't respond.

Dr. McDonough:
Of course, the big question is: Do you think immunotherapy will someday replace the current standard of care?

Dr. Lim:

Immunotherapy, in some situations, hopefully, will replace the current standard of care, but in other situations it probably is going to be part of the armamentarium, and I think our immediate challenge is to figure out where to sequence immunotherapy with current standard of care. For example, in glioblastoma, Dr. Grossman here showed that when patients get conventional radiation, which is a high fraction of treatment, patients actually become lymphopenic, and when they become lymphopenic, that's actually a poor prognostic indicator. And intuitively that makes sense that that may be counterproductive for immunotherapy. If you take away the soldiers that are actually killing the cancer cells, then you may make your immunotherapy less potent.

The same goes with the systemic chemotherapy. We found that in our lab, like Temodar, it decreases the number of T cells and actually changes the population of T cells permanently. We found that memory T cells are decreased in number when you give systemic chemo.

Dr. McDonough:
So, there is, there's definitely obviously a lot of uses for this, a big future. As we look at the future and we look at different ways of using immunotherapy and maximizing it, are there ways to anticipate resistant tumor phenotypes as you are approaching these tumors for treatment?

Dr. Lim:
As we've been super excited about the results of the checkpoint inhibitors in certain tumor types, especially with melanoma, I think we've come to the realization that, again, tumors are very smart and they evolve over time. There was a recent paper that was published in the *New England Journal* where they actually looked at the mechanisms of resistance, and it turns out that there are certain types of tumor cells that have defects in the antigen-presenting machinery -- for example, the beta 2 microglobulin mutations -- and there are other patients who have tumors that have mutations in the interferon gamma pathway, particularly some of the Jak-STAT protein. And interferon gamma is very important in upregulating PD-L1. And the MHC complex is very important for the T cells in order for the T cells to recognize the cancer cells and to dock to the cancer cells. So, I think that as we start figuring out immunotherapy approaches, we have to start anticipating possible mechanisms for resistance.

Dr. McDonough:
The other question I have is: Just as a widespread use, do all tumors respond to immunotherapy?

Dr. Lim:
Not all tumors do respond to immunotherapy. If you look, for example, prostate cancer and pancreatic cancers, pancreatic cancers do not respond to immunotherapy. Try to understand why they are not responsive. I think the bottom line is we don't really know. But as an example in pancreatic cancer, many people believe that pancreatic cancers have such a fibrous tumor that it creates a physical barrier

for T cells to come in. And there was a very neat paper I think that was published out of WashU in *Nature Medicine* where they looked at altering a protein called focal adhesion kinase. Focal adhesion kinase is important in creating this fibrous structure in pancreatic cancer. And when they modified the activity of this focal adhesion kinase, they were able to make a tumor that was resistant to PD-1 now sensitive to PD-1.

Dr. McDonough:
I wanted to ask you one last question. It's a important one in the sense that we talked about a lot of things. Is there something that you wanted to address that you think is important that we didn't talk about?

Dr. Lim:
I think that with immunotherapy, one of the things that we probably have not appreciated as much is the fact that there are external factors that can really affect the way the immune system works or affect the antitumor activity. As I alluded to earlier, what you eat, for example, the microbiome, can enhance the antitumor activity of the immune system. In addition, it turns out that necrosis or hypoxic conditions can also profoundly affect the way the tumors behave. And lastly, with the pancreatic cancer, the actual physical stroma of the tumor could affect the way the T cells work. So, I think as we start thinking about ways to enhance immunotherapy, we should think about, perhaps, altering external factors as well as trying to just modify the activities of the T cells themselves.

Dr. McDonough:
I want to thank our guess, Dr. Lim, for discussing GBM and emerging immunotherapeutic agents on the horizon for this disease. Thank so much for taking the time to join us.

Narrator:
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