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https://reachmd.com/programs/cme/addressing-barriers-in-managing-iraes-associated-with-immune-checkpoint-inhibitor-therapy/12019/

Released: 11/25/2020
Valid until: 11/25/2021
Time needed to complete: 15 minutes

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Addressing Barriers in Managing IRAEs Associated with Immune Checkpoint Inhibitor Therapy

Announcer:
Welcome to CME on ReachMD. This activity, entitled “Addressing Barriers in Managing IRAEs Associated with Immune Checkpoint Inhibitor Therapy” is provided by Prova Education and is supported by an independent educational grant from Bristol Myers Squibb.

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Dr. Davies:
Immunotherapy approaches involving immune checkpoint inhibitors have revolutionized the treatment of various cancers. These agents, however, are known to cause immune-related adverse events, also referred to as IRAEs, which may affect different organ systems with variable clinical presentations. Notably, serious IRAEs, such as pneumonitis and cardiotoxicities, pose significant hurdles in achieving optimal responses and represent a huge clinical challenge for many healthcare professionals.

This is CME on ReachMD, and I’m Dr. Marianne Davies.

Dr. Brahmer:
And I’m Dr. Julie Brahmer.

Dr. Davies:
So welcome, Julie. We have a lot of important content to cover, so let’s dive right in. Dr. Brahmer, can you please discuss the patterns of IRAEs with CTLA-4 and anti-PD-1 agents?

Dr. Brahmer:
So, typically, for CTLA-4 and PD-1 agents, the side effects will occur over the first couple of months, and certainly, depending on the agents that you use, may have actually impacts on the different patterns. Certainly as single agents, ipilimumab is more associated with rash and colitis. And then for nivolumab, pembrolizumab, and other PDL-1 antibodies, such as durvalumab and atezolizumab, and even cemiplimab, these sort of drugs tend to not have the incidence of colitis compared to ipilimumab, but certainly you can see these type of side effects as well. Again, most of these side effects occur within the first six months on either agents. And then longer term, you can see some hypothyroidism occur longer term, as well as pneumonitis occur longer term. And then, occasionally, you should always expect that immune-related toxicities can occur, even when we stop these type of therapies.

For ipilimumab and nivolumab, when we combine these type of drugs, such as for non-small cell lung cancer, the risk of toxicities, really, we do see this increasing, and the type of toxicities where we have to stop therapy and hold the drug and then start on steroids occurs more often compared to the single agents. Certainly the mechanism of actions are slightly different between ipilimumab and the PD-1 or PD-L1 inhibitors. Blocking different checkpoint pathways does have an effect on the different patterns of side effects.

Dr. Davies:
And I think another thing to keep in mind is that if patients are getting combination chemotherapy or cytotoxic agents in addition to the immune checkpoint therapy, that pattern of the developing of side effects may vary, and that can help one to differentiate between

whether it's a cytotoxic side effect versus an IRAE.

Dr. Brahmer:
So, how do we differentiate an IRAE versus other potential causes of a patient's symptoms? Dr. Davies, what do you do in clinic?

Dr. Davies:
So that's a really great question. Part of the way we differentiate is that each disease site or organ-specific disease, when it progresses, depending on where the sites of disease or metastatic lesions are, may have different types of symptoms. But really the key to differentiate IRAEs is to rule out all other causes, such as disease progression or other comorbid medical conditions or other factors such as infection. So first, we consider the timing and the intensity of the onset of the symptoms. Once other causes are ruled out, the toxicity is managed according to IRAE clinical practice guidelines. So for instance, for a patient with lung cancer that comes in with increased dyspnea, we want to rule out disease progression, pulmonary embolus, pleural effusion, infection, or IRAE. Some of the other considerations are to evaluate for risk factors, such as does the patient have an underlying autoimmune disease, or a subclinical inflammation, or have they had an allogeneic stem cell transplantation.

So the criteria to evaluate IRAEs are – we use the CTCAE, or the common terminology criteria for adverse events. And this really provides a common language for us to help measure the severity of toxicity and guide intervention. So general clinical manifestations are usually fatigue and arthralgias. Many toxicities may be asymptomatic, noted on laboratory abnormalities only. And organ-specific toxicities are really specific to that organ. For instance, GI toxicities may present with abdominal cramping or increase in loose stools. Or pulmonary may present with increased oxygen requirements or increased level of dyspnea.

So overall in terms of how we manage these, in general, anti-CTLA-4 therapy has higher overall toxicities profiled both in low-grade and higher-grade. Most notably, higher grade toxicities for GI toxicity with diarrhea and colitis, followed by the PD-1 inhibitors, and then with much lower rates with PD-L1 agents. In terms of fatal toxicities, CTLA-4 deaths are most attributed to colitis and hepatitis, while anti-PD-1 and PD-L1 deaths are attributed to pneumonitis, hepatitis, and neurologic toxicities.

Dr. Brahmer:
I think certainly for these, trying to evaluate patients in the clinic, it can be difficult, particularly even in our lung cancer patients now that COVID is also in the mix of potentially being a cause for infiltrates on a CT scan. It's always something to have in mind when we're seeing patients, that certainly this could be something else other than just pneumonitis.

What are some of the key guidelines for monitoring and treating, as well as managing IRAEs?

Dr. Davies:
Several clinical practice guidelines have been developed to help guide the management of IRAEs, such as those through the National Comprehensive Cancer Center, the Society for Immunotherapy and Cancer, and the American Society of Clinical Oncology. In general, treatment guidelines are best based on the grade, using the CTCAE criteria. Grade 1 is the lowest, in which a patient may be asymptomatic or with mild symptoms or diagnostic or laboratory changes only. Intervention is not indicated, and immune checkpoint inhibitor therapy may continue. In general, grade 2 is with more moderate symptoms, grade 2 diagnostic abnormalities, and intervention may be indicated, such as supportive organ-specific treatment and holding immune checkpoint inhibitor therapy. Grade 3 is more severe, which may be medically significant but not life-threatening. Immune checkpoint therapy is held and in many cases might have to be permanently discontinued. Patients will require hospitalization in some cases and treatment with corticosteroids. Grade 4 toxicities are life-threatening, which require more advanced management. Immunosuppressant therapy is the mainstay of managing these toxicities with corticosteroids. Oral prednisolone may be used for lower grade toxicities, while intravenous methylprednisolone will be necessary for higher grade. In general, the dose is about one milligram per kilogram per day. And this continues until the toxicity is decreased to a grade 1. At this point, the steroid can be tapered over a 4- to 6-week course, as a more rapid taper may lead to the flare of the toxicity. If there is no improvement in the toxicity in several days, we may need to consider the addition of another immunosuppressant agent, such as infliximab or mycophenolate.

So keeping that in mind, what are some optimal strategies for managing IRAEs per specific types?

Dr. Brahmer:
Well, I think probably the one side effect that I want to go over that we see probably more often than not is diarrhea or colitis. So, for colitis, in a patient who is undergoing immunotherapy, we have to evaluate them for other causes, obviously, but really the treatment depends on grade. If patients are minimally symptomatic, you have what they have baseline bowel movements per day, and if they're less than a 4-bowel-movement-per-day increase, then you can consider holding immunotherapy and just asking them to take antidiarrheal medications. If they start having symptoms, such as cramping or bleeding, that is actually grade 2 colitis, and holding

immunotherapy is key, and starting oral corticosteroids. If patients do not improve within 2 to 3 days, you have to think about adding other medications such as infliximab to your regimen to try to get the colitis under control. And obviously, if patients are unable to maintain oral intake or become dehydrated, this increases the grade, and patients may require hospitalization or IV corticosteroids.

I think one other toxicity to kind of highlight, while it is uncommon, in some patients we do see cardiotoxicity. Cardiotoxicity can also be seen in a syndrome of also seeing myositis, as well as you can also see patients have myasthenia gravis kind of as 3 different type of IRAEs that tend to go together. So it's just something to keep in mind. If someone presents with myasthenia gravis type of symptoms, to think in the back of your mind make sure checking a troponin, as well as the CPK [creatine phosphokinase] for the muscles that these type of side effects can occur all together.

When you diagnose cardiac toxicity, if they have high troponins, we actually start right off the bat with high doses of corticosteroids in these patients. And these patients are obviously admitted. And we get the subspecialists such as the cardiologists that are familiar with these type of side effects, such as those physicians who are specialists in cardiomyopathies, we get them involved as well. And then, if someone has cardiac toxicity, it would be very rare for us to restart immunotherapy in these patients.

Now, in my clinic, we see a lot of pneumonitis, so for pneumonitis if patients are asymptomatic and just have changes on the CT scan, we will continue therapy and monitor them closely. Obviously, if they start becoming hypoxic or symptomatic, then we'll hold immunotherapy and start oral corticosteroids, usually a milligram per kilogram of oral prednisone. But if they start requiring oxygen and need to be admitted, then clearly we get our pulmonologist involved to rule out other causes, as well, and put these patients on IV corticosteroids. Again, restarting immunotherapy in this case really depends on the patient and the grade. Again, high-grade pneumonitis, or even pneumonitis that takes a long time to taper the steroids beyond six weeks, then we may not restart the immunotherapy. But certainly, there's a lot of other toxicities that we could talk about, but looking at the guidelines that you feel most comfortable with and following those certainly can help.

Dr. Davies:
Thank you, Dr. Brahmer, that is really helpful. And I think some of the keys here are that now more than ever with immune checkpoint adverse events, we are needing to consult with our subspecialists in the management because there are such unique strategies for managing each organ-specific toxicity. And another good point you brought up is that oftentimes, some of these refractory and more significant toxicities may require a longer steroid taper. And patients may not be able to fully come off of immunosuppressant therapy, so they may be on lower doses of steroids for a longer period of time to keep that toxicity under control.

Well, this certainly has been a fascinating conversation, but before we wrap it up, Dr. Brahmer, can you share with our audience your one take-home message?

Dr. Brahmer:
My take-home message for our audience would be that – actually three take-home messages – would be monitor for these type of toxicities, expect them and treat them quite quickly. And talking with your patient will help you decide whether or not it's right to restart immunotherapy if you do develop toxicities.

Dr. Davies:
Absolutely. And I think in general, we need to stress with our patients that, in general, immune checkpoint therapy is well tolerated. The toxicities are typically well controlled with immunosuppressant therapy, and the key is close communication to assure that we have a swift diagnosis of the toxicity and to minimize the progression to before it progresses to a more severe toxicity. And in many cases, free treatment may be possible.

So unfortunately, that's all the time we have today. So I want to thank our audience for listening in and thank you, Dr. Brahmer, for joining me and for sharing all of your valuable insights. It was great speaking with you today.

Dr. Brahmer:
Thanks so much, Dr. Davies.

Announcer:
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