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Case 6: Implementing Current Guidelines and Best Practices for Monitoring and Mitigating Immune-Related Adverse Events

Announcer:
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Dr. Reuss:
Hello, my name is Joshua Reuss. I'm a Thoracic Medical Oncologist and Assistant Professor of Medicine at Georgetown Lombardi Cancer Center in Georgetown University School of Medicine. And in today's session, we are going to discuss implementing current guidelines and best practices for monitoring and mitigating immune-related adverse events.

So to begin with two parallel cases. On the left, we have Mr. N. This is a 74-year-old male with a history of chronic atrial fibrillation on apixaban, who is receiving adjuvant anti-PD-1 immunotherapy in sequence following adjuvant chemotherapy for resected stage IIB non-small cell lung cancer. He presents for cycle 5 of therapy without complaints, but CT imaging reveals new nonspecific ground-glass opacities of the right middle lobe. In clinic, his vital signs are stable, but he reports a subtle change in dyspnea on exertion over the past few weeks. What is your recommended approach here?

On the right we have a different case. This is 77-year-old female with a history of hypertension, hyperlipidemia, and type 2 diabetes, who is currently receiving maintenance therapy with pemetrexed and pembrolizumab for stage IV non-small cell lung cancer with excellent response. She presents to clinic for an unscheduled visit for dyspnea 9 days after receiving her 8th cycle of maintenance pembrolizumab. She reports one week of worsening dyspnea and can only walk 5 feet before needing a break. She also reports worsening dry cough. She denies fevers or substernal chest pain. In clinic, she desaturates from 96% to 91% on room air when ambulating 5 feet, and this is associated with dyspnea.

So immune-related adverse events associated with immune checkpoint blockade, this is a novel type of adverse event associated with immunotherapy. And when I describe this to my patients, I say that really the immunotherapy works by activating the immune system to fight cancer. But sometimes the immune system can get a little too jazzed up and go after normal areas of the body and cause inflammation there. And so that's what's shown on the left side of the screen here, where you can have inflammation in almost any area of the body ranging from rash, dermatitis to pneumonitis, inflammation in the lungs, colitis, inflammation in the gut, to some of the more really scary adverse events such as myocarditis, inflammation in the heart, or meningitis or encephalitis picture in the brain.

And in terms of the mechanism of how immunotherapy-related adverse events occur, there are really multiple proposed mechanisms ranging from pre-existing auto antibodies, increased T cell activity, as well as complement-mediated inflammation as well.

So, immunotherapy toxicity management, there are really multiple key pillars here. We really don't know the best ways to prevent immunotherapy-related side effects. But definitely anticipation and monitoring is incredibly important, because you want to detect these adverse events early so that optimal treatment can be implemented before we get to a high-grade, more serious scenario.

Importantly, the timing of these immune-related adverse events is quite heterogeneous. You could see here for PD-L1 monotherapy,

PD-1 monotherapy on the top, the range of when these adverse events tends to occur varies from, you know, just a couple of weeks after initiation of therapy to up or up over a year, both for all-grade and for high-grade adverse events. And you can see the timing also differs somewhat with the combination of the PD-1 plus CTLA4 inhibitor, as well as the frequency of these adverse events. Though it is important to note that immune-related adverse events can really occur at any time after the initiation or cessation of immunotherapy. So one has to really be on high alert in terms of being aware and anticipating the emergence of such a toxicity.

Here's just a further slide illustrating the timing of onset and resolution of, of immune-related adverse events for both PD-1 monotherapy and combination therapy. And you can see that the incidence of adverse events involving the GI and hepatic systems really appears to increase with the addition of CTLA4 inhibitor.

Shown another way, this is the frequency of immune-related adverse events from the POSEIDON study of durvalumab plus tremelimumab and chemotherapy, compared to durvalumab plus chemotherapy alone. And you can really see on this tornado plot where there is increased frequency and intensity, primarily of the GI-related toxicities, though increased severity of other adverse events such as pneumonitis and renal toxicity has also been observed.

So the workup of immune-related adverse events and management is incredibly complex and requires multidisciplinary input. Workup should be organ dependent and of course requires an assessment of other common etiologies. So with pneumonitis, you have to look for infection. Or is this disease progression? These are important considerations. Importantly, these can occur days to years after immunotherapy initiation and cessation. And so we need to be on high alert for the manifestation of these toxicities. Fatal toxicities, when they occur, tend to happen early after immunotherapy initiation. And most common, so PD-1 monotherapy, pneumonitis, hepatitis, and neurotoxicity. And for the combination, colitis and myocarditis can be seen.

The initial management tends to be similar across immune-related adverse events, typically with prednisone or methylprednisolone, 1 to 2 mg/kg. But in the setting of steroid-refractory adverse events, that's where you start to get some variability depending on the organ system that's involved. And importantly, a case-by-case decisions should be utilized when considering resumption of immunotherapy, that should take into account side effect severity, disease status, prognosis, and patient/provider preference. But I cannot stress enough the importance of multidisciplinary input and really utilizing those subspecialties to the best of your ability.

This is just another slide outlining the management of immune-related adverse events and showing how, for low-grade symptomatic management and with ongoing immunotherapy is usually acceptable. But when you get to grade 2 to grade 3, that's when stopping therapy and initiating oral steroids, or if hospitalization is required, IV steroids, and then involving subspecialty management for this really complex workup and treatment decision-making.

So when can you resume immunotherapy after resolution of an immune-related adverse event? I think this is all retrospective data here and this should definitely be a patient- and provider-guided decision. You can see here on the right, some data on the recurrence rate for immune-related adverse events after resumption of immunotherapy, which on the whole, probably occur at a rate of 20 to 30%. But there should be very important considerations here, including the type of immune-related adverse event, you're probably more likely to resume immunotherapy for a low-grade pneumonitis or thyroiditis as opposed to myocarditis, for example, the severity of immune-related adverse event, what's the setting of therapy? Is this adjuvant or is this someone with metastatic disease? What is their treatment response? What are their comorbidities? And what are their goals?

Importantly, we know that those who experience immune-related side effects may have a more pronounced benefit. This is a pooled analysis from several of the IMpower studies showing how those who developed immune-related adverse events, both importantly in the immunotherapy-containing arm but also in the control arm, appeared to have improved survival. And we've seen that this benefit can be durable and outlast even in the setting of cessation of immunotherapy for side effects. So this could at least give providers and patients some degree of reassurance if they need to stop immunotherapy for a side effect, that those benefits may outlast the duration of the therapy.

So to revisit our cases, first on the left, our case of a patient where CT findings were appreciated, potentially for low-grade pneumonitis, though maybe with some subtle change in dyspnea. So for this patient, in the setting of possible worsening dyspnea, grade 1 or grade 2, immunotherapy was held for a week for a pulmonology evaluation, PFTs and a 6-minute walk test were without significant changes from baseline, and the patient was subsequently resumed with immunotherapy without worsening of symptoms.

On the right, this was obviously a much different scenario, a high-grade toxicity with exertional hypoxia, so at least a grade 3 adverse event. This patient was hospitalized for further workup and while a CTPA was negative for PE, there was worsening diffuse ground-glass opacities throughout all 5 lobes of the lung. Cardiac workup was negative without EKG changes. There was no BNP or troponin elevation. Infectious workup was negative. This patient was started on IV methylprednisolone with rapid improvement. She was discharged on prednisone taper, and not resumed with immunotherapy.

So briefly, I want to touch on one additional case for an important immune-related adverse event. This is a 67-year-old gentleman with a history of hypertension, hyperlipidemia, and type 2 diabetes, who started adjuvant atezolizumab after receiving 4 cycles of adjuvant platinum-based chemotherapy for a resected stage IIB non-small cell lung cancer. Two weeks after receiving the initial dose of atezolizumab, this patient presented with worsening fatigue, shortness of breath, and tachycardia with a heart rate of 145. But his vital signs were otherwise stable, but lab showed a new AKI, low-grade anemia, thrombocytopenia, and transaminitis. He was directed to the ER for workup, where EKG showed tachycardia with an incomplete right bundle branch block. CTPA was negative for PE, pneumonitis. Troponin and BNP were within normal limits. The patient was hospitalized and, importantly, a TTE showed a new drop in ejection fraction to 25 to 30% with a severe global hypokinesis. Cardiac MRI revealed patchy myocardial inflammation diffusely involving the left ventricular myocardium without evidence of pericardial inflammation. Left and right heart catheterization with endomyocardial biopsy revealed stable 3-vessel coronary artery disease, and the biopsy showed lymphohistiocytic infiltration consistent with myocarditis.

So MACE, or major adverse cardiac events, with immunotherapy are important and I think underrecognized side effect of immunotherapy. In pooled clinical trial data ICI-related MACE occurs at about 0.6%, but the majority are high grade. The incidence is higher with PD-1 combination strategies compared to single agent, and this can importantly present not only with myocarditis, but as a triad with myositis and myasthenia, so very severe and potentially life-threatening toxicities that weren't immediate management. And so how do we tend to manage these patients? So first and foremost, discontinuing immunotherapy. High-dose steroids, and depending on the grade, one can sometimes get away with 1 to 2 mg/kg of IV methylprednisolone, though typically initially one will start 1 gram per day of IV methylprednisolone, while - if MACE, high-grade myocarditis is on the differential, you definitely would rather start.

And then the workup is important, right? You need to look for an MI, potentially with cardiac catheterization, cardiac MRI is important as well. But if myocarditis is ultimately suspected as the likely diagnosis, oftentimes, if there is no improvement on steroids, one does need to consider additional therapies such as mycophenolate, IVIG, or other treatments. And involving cardiology is super important here.

So back to this patient, he was actually fortunate to have a relatively early-grade myocarditis without significant symptoms. He was started initially on an empiric 1 gram per day of methylprednisolone with close consultation with cardiology, and following the cardiac MRI results. Given stability, he was transitioned to 1 mg/kg BID of methylprednisolone, and ultimately transitioned to 1 mg/kg per day methylprednisolone and prednisone taper. His cardiac function ultimately returned to baseline. And importantly, atezolizumab was permanently discontinued.

So in summary, immune-related adverse events can affect any organ system and any time after administration of immunotherapy. Close surveillance for the emergence of immune-related adverse events is important in order to institute prompt management. Severe and complicated immune-related adverse events do truly warrant multidisciplinary input; this is critical to optimal management of patients. And a decision as to whether or not to resume immunotherapy after an adverse event is complex, and factors that should be taken into account includes severity of the toxicity, clinical benefit of therapy, the setting of therapy, so metastatic versus neoadjuvant or adjuvant, patient comorbidities, and then patient/provider preference.

And so with that, I want to thank everyone for their attention. And with that, we'll conclude this session. Thank you.

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