Immune Checkpoint Inhibitors: Common Questions About Uncommon Adverse Events

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Presenter's disclosure of conflicts of interest is found at the end of this article.

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Abstract

At JADPRO Live Virtual 2020, Lisa Kottschade, APRN, MSN, CNP, highlighted considerations for advanced practitioners on the recognition and monitoring of rare and life-threatening immune-related adverse events (irAEs), as well as strategies for managing patients who have corticosteroid-refractory irAEs.

Immune checkpoint inhibitors have been successful in advancing the field of oncologic treatment, but there is a dark side to these drugs. Immune-related adverse events (irAEs) that occur via activation of a patient's immune system can affect any tissue, organ, or body system and pose distinct challenges from traditional chemotherapy.

During JADPRO Live Virtual 2020, Lisa Kottschade, APRN, MSN, CNP, of Mayo Clinic, discussed special considerations for patients initiating therapy and undergoing rechallenge with immune checkpoint inhibitors (Table 1). Ms. Kottschade also discussed the recognition and management of rare and life-threatening irAEs

RISK FOR IMMUNE-RELATED ADVERSE EVENTS

As Ms. Kottschade explained, immune checkpoint inhibitors are cancer treatment strategies that are directed at improving the host immune response to cancer, and which target immune checkpoint molecules. Their unique mechanism of action poses a risk for irAEs that can affect any organ system. Careful consideration should be given to populations that may be more at risk should they experience an irAE. These include history of autoimmune conditions, transplant population, use of concurrent steroids or other immunosuppressants, poor liver, renal, lung, or cardiac function, chronic viral infections, vaccine use, recent antibiotic use, and previous irAEs from checkpoint inhibitors.

Autoimmune Conditions

Patients with preexisting autoimmune conditions have traditionally been excluded from immune checkpoint inhibitor clinical trials. In

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Table 1. Clinically Available Immune Checkpoint Inhibitors

Anti–PD-1	Anti–PD-L1	Anti-CTLA4
Pembrolizumab	Atezolizumab	Ipilimumab
Nivolumab	Avelumab	
Cemiplimab	Durvalumab	

clinical practice, however, patients who are not on chronic immunosuppression are generally considered for immunotherapy. Based on retrospective series, response rates may be lower, said Ms. Kottschade, but it is still a treatment that may be available to them (Abdel-Wahab et al., 2018).

Transplant

Patients who have undergone solid organ transplant are often on high doses of immunosuppression to prevent rejection of that transplant, and there is concern of loss of the transplant organ with the use of immune checkpoint inhibitors.

"We need to have very frank conversations with patients regarding the risk-benefit ratio," said Ms. Kottschade. "We have very little data in this population."

Vaccination

Early clinical trials disallowed vaccination while on study. Although a small study from Switzerland described an unexpectedly high rate of irAEs, a recent retrospective review showed no increase in such events in 370 patients on immune checkpoint inhibitors vaccinated for influenza (Chong et al., 2019). Inactivated influenza is generally considered safe, said Ms. Kottschade, but there are currently no data on other vaccines. It's generally recommended not to administer live-attenuated vaccines immediately before, during, or immediately after immune checkpoint inhibitor therapy.

Antibiotics

Although the data are still limited, antibiotics have been shown to affect the outcomes of immune checkpoint inhibitors. A headline-producing study of 195 patients with cancer starting on immune checkpoint inhibitors who had received pretreatment antibiotics prior to receiving immunotherapy showed lower survival rates, according to Ms. Kottschade, who noted that survival was somewhat improved for patients receiving concurrent antibiotics (Pinato et al., 2019). The paper has been criticized, however, due to the poor underlying performance status and comorbidities of the patient population.

Rechallenge of Immune Checkpoint Inhibitors

For patients taken off immune checkpoint inhibitors due to irAEs, questions remain about whether to rechallenge in those who were responding. A cross-sectional analysis was performed of more than 20,000 irAEs, for which 6,000 underwent rechallenge. There were 452 that had available post-challenge data, which showed approximately 131 recurrences of the original adverse event (Dolladille et al., 2020). The most common recurrent irAEs were colitis, hepatitis, and pneumonitis. Most patients who had been on dual checkpoint inhibitors were rechallenged with just the PD-1 inhibitor alone, which is standard clinical practice.

LESS COMMONLY REPORTED IMMUNE-RELATED ADVERSE EVENTS

Next, Ms. Kottschade discussed less commonly reported irAEs and highlighted their breadth (Table 2).

Renal Toxicity

The most common renal side effect is acute interstitial nephritis, with an incidence rate between 2% and 5%. Patients can be anywhere on the spectrum from asymptomatic with just a creatinine elevation, to a triad of fever, rash, and eosinophilia. There have also been cases of glomerulonephritis reported.

Workup involves ruling out other etiologies, such as hydronephrosis, infection, dehydration, or recent IV contrast. Providers should also assess for renal toxic medications.

Treatment is based off the severity of the renal dysfunction. For patients who have mild creatinine increases, immunotherapy is put on hold, and they are followed with labs and a urine protein to creatinine ratio (UPC) test. Patients with moderate renal dysfunction should start prednisone and consult with nephrology. Those with severe dysfunction often need to be admitted to the

hospital and treated with high-dose prednisone. These patients may need a renal biopsy too, said Ms. Kottschade.

Ocular Toxicity

The two main ocular adverse events are uveitis and episcleritis. Patients can present with blurred vision, photophobia, tenderness/pain, eyelid swelling, redness, and proptosis.

Treatment depends on the severity of symptoms. For mild symptoms, ophthalmology typically uses artificial tears, but for uveitis, ocular steroids and occasionally systemic steroids are used in this patient population.

Pancreatic Toxicity

Pancreatitis generally presents with classic symptoms, although patients may have isolated radiologic findings or lab elevations only. Workup involves obtaining pancreatic enzymes, IgG4, and a CT image of the abdomen.

For patients with mildly elevated enzymes but no radiologic findings, treatment entails observation alone. If patients are asymptomatic but have radiographic findings, treatment with prednisone (1 mg/kg) can be done in the outpatient setting. Patients who are symptomatic generally need to be admitted for IV fluid, bowel rest, and high-dose steroids.

LIFE-THREATENING IMMUNE-RELATED ADVERSE EVENTS

During her presentation, Ms. Kottschade highlighted the complexity of managing life-threatening iraEs and offered some clinical pearls for advanced practitioners.

Pneumonitis

Patients often present with focal or diffuse inflammation of the lung parenchyma, which is typically identified on CT imaging, but they may present asymptomatically too (only seen radiographically). Others present with dyspnea on exertion, shortness of breath at rest, and/or orthopnea. Approximately 50% of patients have a dry, nagging cough. Many also experience chest pain. According to Ms. Kottschade, the differential should rule out pulmonary embolism, progression of disease, and infection, especially during the pandemic.

Table 2. Less Commonly Reported Immune-Related Adverse Events

Endocrine	Pulmonary
• Diabetic ketoacidosis	• Pneumonitis
• Primary adrenal insufficiency	• ARDS/AIP
• Graves-like disease	• Pleuritis
• Hypercalcemia	• Sarcoid-like reaction
Cardiac	Neurologic
• Myocarditis	• Peripheral neuropathy
• Pericarditis	• Encephalitis
• Vasculitis	• Myasthenia gravis
Renal	• Guillain Barré
• Nephritis	• Aseptic meningitis
Ocular	Hematologic
• Uveitis	• Thrombocytopenia
• Episcleritis	• Hemolytic anemia
Rheumatologic	• Aplastic anemia
	Musculoskeletal
	• Myositis
	• Arthritis

The diagnostic workup involves a CT scan of the chest and pulse oximetry (both at rest and walking). For patients with grade 2 symptoms or higher, an infectious workup involving nasal swab, sputum culture, blood culture and sensitivity, and urine culture is recommended. Providers may also need to consult pulmonology for consideration of bronchoscopy.

For patients who have very mild symptoms, the recommendation is for providers to hold immune checkpoint inhibition, continue to check pulse oximetry, and repeat the CT scan in 3 to 4 weeks. With improvement of symptoms, a rechallenge is considered in this patient population. For moderate symptoms, a consult with pulmonology and an infectious workup are needed. These patients will also require steroids.

Patients who present with grade 3 or 4 symptoms will require hospital admission and will be treated with higher-dose steroids, said Ms. Kottschade. If symptoms do not improve in 2 to 3 days, treatment with mycophenolate or infliximab is recommended. It is likely that these patients will not be rechallenged with immune checkpoint inhibitors.

Neurotoxicity

The incidence of neurotoxicity is 3.8% for CTLA-4 inhibitors, 6% with PD-1 inhibitors, and 12% with combination therapy (Brahmer et al., 2018). Because of variable presentation and nonspecific symptoms, said Ms. Kottschade, there is a wide

range of differentials, including worsening disease and infection. The time to onset of symptoms ranges from 3 days to 17 months, but the median time is approximately 6 weeks.

The workup involves an MRI of the brain and spine, lumbar puncture, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), antineutrophil cytoplasmic antibody, paraneoplastic panel, infectious workup, acetylcholine receptor antibodies, and possible electromyography. Neurology should also be consulted immediately, said Ms. Kottschade.

For severe grade 3 or 4 neurotoxicity, patients should be hospitalized and receive high-dose steroids. Plasmapheresis may also be used. For patients who do not respond, IV immunoglobulin or rituximab should be considered.

Cardiac Toxicity

Immune checkpoint inhibitors are associated with myocarditis, pericarditis, or cardiomyopathy. Although incidence rates vary widely, there has been an increase in cardiac toxicity with the use of dual checkpoint inhibition. The one thing to remember is that once patients become symptomatic, there is an approximately 50% fatality rate, said Ms. Kottschade.

Standard cardiac workup is to rule out any ischemic event and includes troponins, creatine kinase (CK) and B-natriuretic peptide (BNP) levels, ESR, and CRP. An electrocardiogram is also used to assess for ST-T wave abnormalities and new arrhythmias, and an echocardiogram is used to assess for left ventricular systolic dysfunction, regional wall motion abnormalities, increased wall thickness, pericardial effusion, and strain abnormalities. If the echocardiogram is inconclusive, providers should consider cardiac MRI and possible cardiac biopsy.

Patients experiencing cardiac toxicity need to discontinue their immune checkpoint inhibitor and start high-dose steroids, and need to be hospitalized, said Ms. Kottschade, who noted that there are no data regarding rechallenging in this patient population.

Triple "M" Syndrome

Myasthenia gravis, myositis, and myocarditis often present together as a triad of side effects. Patients with this syndrome present with fatigue and weakness, and they may have ocular or bulbar symptoms. In addition, they frequently have respiratory symptoms and chest pain.

"Early detection is key here," noted Ms. Kottschade. "There is a high fatality rate with this syndrome."

MULTIDISCIPLINARY TEAM APPROACH

Finally, Ms. Kottschade emphasized that when caring for patients with irAEs or those being treated with immune checkpoint inhibitors in general, it's essential to have a multidisciplinary team approach that is patient centered. Members of the multidisciplinary care team include medical oncologists, advanced practitioners, oncology nurses, primary care, and specialists. Pharmacists are also very helpful when trying to decipher what medications might be nephrotoxic or hepatotoxic in patients who are experiencing those side effects. ●

Disclosure

Ms. Kottschade had no conflicts of interest to disclose.

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