ABSTRACT

With the increased use of immune checkpoint inhibition (ICI) comes an increase in the number of patients being treated for immune-related adverse events (irAEs). At the NCCN 2023 Annual Conference, presenters discussed 3 different types of irAEs, namely immune-mediated pneumonitis, major adverse cardiac events including myocarditis and myositis/myasthenia gravis overlap syndrome, and oral toxicities including mucositis and sicca syndrome. They emphasized the importance of considering comorbidities and infectious causes when treating immune pneumonitis. In the context of cardiac events during ICI therapy, the presentation highlighted the need for early detection and vigilance in recognizing insidious, nonspecific symptoms, particularly in cases involving myocarditis with myositis/myasthenia gravis overlap syndrome. Finally, the increasing recognition of oral toxicities was discussed, in addition to the importance of timely intervention to prevent long-term morbidity.

Immunotherapy has emerged as the fourth pillar of cancer treatment, beyond surgery, radiation, and chemotherapy, offering new hope and improved outcomes for patients. However, with its increasing use, managing the potential side effects and complications associated with immunotherapy has become a critical aspect of patient care.

During the NCCN 2023 Annual Conference, Marianne Davies, DNP, MSN, RN, ACNP-BC, AOCNP; Jordan McPherson, PharmD, MS, BCOP; and John A. Thompson, MD, discussed how to improve the time to recognition of immune-related adverse events (irAEs), including pneumonitis, myocarditis, and oral toxicities, as well as how to initiate appropriate treatment. Joining the presenters was John A. Thompson, MD, Medical Director, Phase I Clinical Trials Program, Fred Hutchinson Cancer Research Center, and Chair, NCCN Guidelines Panel for Management of Immunotherapy-Related Toxicities Panel, discussed how to improve the time to recognition of immune-related adverse events (irAEs), including pneumonitis, myocarditis, and oral toxicities, as well as how to initiate appropriate treatment. Joining the presenters was John A. Thompson, MD, Medical Director, Phase I Clinical Trials Program, Fred Hutchinson Cancer Research Center, and Chair, NCCN Guidelines Panel for Management of Immunotherapy-Related Toxicities, and together they reviewed irAEs caused by immune checkpoint inhibitor (ICI) therapy and highlighted key components of clinical management.

Cancer Immune Cycle

As Dr. Davies explained, the cancer immune cycle involves the release of tumor antigens, priming and activating T cells, infiltration into the tumor microenvironment, and the killing of cancer cells. However, blockades created by tumor cells can disrupt this process. The development of CTLA-4, PD-1/PD-L1, and LAG-3 inhibitors have dramatically expanded cancer treatment options in the decade since the 2011 FDA approval of the first anti-CTLA-4 agent, ipilimumab. Since then, there has been a significant increase in both the number of ICI agents approved and the number of approved indications as both monotherapy and in combination with other agents.

As of March 2023, there were 11 approved ICIs, with the addition of a LAG3 inhibitor and another PD-1 inhibitor. These agents have been approved for use in various settings, including metastatic relapse, first-line treatment, and adjuvant and neoadjuvant settings. Common toxicities include fatigue, pruritus, rash, nausea, and vomiting, but continuous monitoring for side effects is necessary throughout treatment, because specific irAEs may affect any organ system, are highly unpredictable, and vary in their timing from start of therapy.

Pulmonary Toxicity

Dr. Davies recommended the use of an algorithm designed by Chanpia et al., which includes prevention, anticipation, detection, treatment, and monitoring for immune-related toxicities. In the context of immune-mediated pneumonitis, key aspects of this stepwise approach include encouraging smoking cessation for all patients; ensuring that vaccinations are up-to-date; assessing baseline symptoms, such as cough and oxygen requirements; educating patients to report any new or
worsening symptoms; and regularly assessing patients’ oxygenation status at rest and during ambulation.

Early signs of pulmonary complications may include changes in oxygen requirements, respiratory rate, and breath sounds. Diagnostic tests, such as nasal swabs, sputum cultures, chest radiographs, and CT scans of the chest, can help rule out other potential causes, such as infection, disease progression, pulmonary embolism, or pleural effusion.

Immune-mediated pneumonitis has an incidence of 3%–7% and occurs more frequently with anti–PD-1/L1 agents compared with CTLA-4 inhibitors. With a median onset of 60 to 90 days from the start of ICI therapy, and pneumonitis carries a high mortality rate of 20%–30%, according to Dr. Davies. Patients typically present with dry cough, shortness of breath, chest pain, and increased oxygen requirements.

**Secondary Immunosuppressive Agents**

“Assess patients for travel history to countries with endemic bacterial and viral infections, because this could pose additional risks,” said Dr. Davies. “If patients do not respond to steroids within 48 to 72 hours, additional therapy is recommended, along with close monitoring.”

**Cardiac Toxicity**

As Dr. McPherson explained, ICI-induced myocarditis is a rare but potentially fatal irAE. The median onset for this condition is approximately 30 days from the start of ICI therapy. “Although rare, the mortality rate of ICI-induced myocarditis is high, ranging from 25% to 50%,” said Dr. McPherson. “Patients presenting with non-specific symptoms, such as weakness, muscle pain, dyspnea, and fatigue, should be evaluated for myocarditis and undergo an extensive cardiologic evaluation, including troponins, electrocardiogram (ECG), echocardiogram, B-type natriuretic peptide, and creatine kinase.”

If myocarditis is suspected, the recommended treatment is to pulse the patient with methylprednisolone dosing (1,000 mg intravenously daily for 3–5 days) and transition to lower dosing if they respond. If there is no improvement within 1 to 2 days, secondary immunosuppressants should be initiated. It is important to note that ECG comparison with baseline is recommended, although obtaining a baseline ECG prior to starting ICI therapy is not yet standard practice.

“Patients with suspected myocarditis should be placed on telemetry, admitted to the ICU, and closely monitored due to the risk of arrhythmia-related death,” said Dr. McPherson.

**ICI-Related Major Adverse Cardiac Events**

In a recent study published in the *Journal of Clinical Oncology*, researchers examined ICI-related major adverse cardiac events in a cohort of 7,000 patients. The incidence of ICI-related major adverse cardiac events was found to be 0.6%, with a higher rate in those who underwent combination therapy and targeted therapy. Most (45%) of these events were myocarditis; of note, all 4 deaths reported among the 40 patients with myocarditis were in those noted to have concomitant myositis.

As Dr. McPherson explained, the “three Ms”—myocarditis, myositis, and myasthenia gravis (MG)—are known to occur simultaneously in patients receiving ICI therapy and may lead to life-threatening complications. A 2021 systematic review including 60 patients with these overlapping conditions reported a high mortality rate of 60% in the hospital. Treatment of these patients typically includes cardiology referral, steroids, IVIG, and plasmapheresis, but may also necessitate other secondary immunosuppressants to prevent death.

“It is estimated that 30% to 40% of myocarditis cases may have overlapping syndromes with myositis and MG,” said Dr. McPherson. “Therefore, it is recommended that clinicians evaluate patients suspected of myocarditis for these additional conditions.” In the case of concern for MG, additional early consultation with neurology and testing for acetylcholine receptor antibodies are advised.

**Oral Toxicities**

Finally, Dr. Thompson reported that irAEs related to the mouth have become an increasingly recognized area of concern, which has led to modifications and updates in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Management of Immunotherapy-Related Toxicities. The latest NCCN Guidelines now feature a section addressing oral mucosal inflammation (Figure 1). Key steps for workup from this section include: (1) perform a comprehensive mucosal examination; (2) consider mucosal biopsy if possible and indicated; (3) conduct cultures to rule out infectious causes; and (4) evaluate the potential contribution of cytotoxic therapy.

“As the use of immunotherapy in combination with cytotoxic chemotherapy increases, it is essential to determine the cause of mucositis, whether it is due to chemotherapy or immunotherapy,” said Dr. Thompson. “The updated NCCN Guidelines emphasize the importance of not automatically attributing oral mucositis to cytotoxic therapy and considering the possibility of immunotherapy as a causative factor.”

The NCCN Guidelines also address dry mouth or sicca syndrome, oral disease, and mouth pain. According to Dr. Thompson, it is important to consider that patients...
experiencing dry mouth or sicca syndrome may also have an overlap syndrome involving a rheumatologic process. In such cases, a rheumatology referral or consultation may be necessary, he said.

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References