IMMUNE CHECKPOINT INHIBITORS AND CARDIOTOXICITY

Cardiotoxicities Associated With Immune Checkpoint Inhibitors

- **Myocarditis:** 0.06% to 2.4% of patients receiving immune checkpoint inhibitors (ICIs) experience myocarditis, with a 2x higher risk in incidence and mortality for patients receiving ICIs in combination with immunotherapy.\(^1\)\(^{-3}\) Mortality among these patients ranges from 25% to 50%.\(^2\)\(^{-5}\)
- **Pericarditis:** Incidence of pericardial lesions is 0.3% with median onset 30 days after first dose of ICI. Pericardial disease is the second most commonly reported cardiac adverse event associated with ICIs, representing 7% to 13.6% of ICI-associated cardiotoxicity cases. Can occur in isolation or with ICI-related myocarditis. The mortality rate 21%. Patients with cancer who receive ICIs following radiotherapy to thoracic area might be more prone to pericardial disease.\(^6\)

Patient Risk Factors

- Comorbid autoimmune diseases
- Diabetes mellitus
- Pre-existing cardiovascular disease

Cardiac immune-related adverse events appear more frequently in patients treated with CTLA-4 antagonists compared with PD-1 inhibitors,\(^7\) and the risk increases with combination therapy.\(^3\)\(^{,8,9}\) The development of cardiac immune-related adverse events in patients treated with combination therapy leads to ICI discontinuation in up to 50% of patients.\(^8\)\(^,9\)

Monitoring/Management Strategies

**Myocarditis**

<table>
<thead>
<tr>
<th>Onset and Symptoms</th>
<th>Onset of ICI-associated myocarditis is within 3 months of treatment initiation in 81% of cases,(^2,3) with a median time of 17-65 days after the first dose of ICI.(^1)(^0) Late presentations of up to 454 days have been reported in the literature.(^1)(^1) Symptoms are nonspecific and may include dyspnea, chest pain, fatigue, myalgia, palpitations, syncope, dizziness, or altered mental status.</th>
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<tbody>
<tr>
<td>Diagnostics(^6)</td>
<td>- Baseline electrocardiogram (ECG) and serum troponins(^1)(^2)</td>
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<td>- Check for increased serum troponin</td>
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<td>- ECG to rule out an acute coronary syndrome</td>
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<td>- Echocardiogram</td>
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<td>- Cardiac MRI is diagnostic</td>
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<td>- Endomyocardial biopsy (gold standard)</td>
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Post-Diagnosis

- Withhold ICI therapy
- Serum high-sensitivity cardiac troponin I (hs-cTnT) also used in assessing prognosis (not just diagnosis)
- Brain natriuretic peptide
- ECG
- Transthoracic echocardiogram

Treatment

- Glucocorticoids IV 500-1000 mg then oral prednisone 1-2 mg per kilogram of body weight for 2 weeks with slow taper 10 mg per week thereafter (monitor troponin level during taper); hold ICI
- For acute heart failure: IV diuretics, inotropes, mechanical circulatory support
- Bradyarrhythmias—may require pacemaker

Pericarditis

Onset and Symptoms

- Often nonspecific symptoms
- Shortness of breath, pericardial pain, upper venous congestion

Diagnostics

- Physical exam
- ECG
- Chest x-ray
- Cardiac markers including troponin, erythrocyte sedimentation rate, C-reactive protein
- Cardiac MRI is diagnostic

Post-Diagnosis

- Withhold ICI
- Evaluate for evidence of concurrent ICI-related myocarditis

Treatment

- Colchicine and nonsteroidal anti-inflammatory drugs (NSAIDs)
- Steroids only if unresponsive to NSAIDs. 0.2-0.05 mg/kilogram of body weight (monitor troponin level during taper)
- In steroid refractory, infliximab or anti-thymocyte globulin as second-line therapy
- Pericardial window for cardiac tamponade

References