Cardio-Oncology Updates | *FAST FACTS*

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	
Onset and Symptoms	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.[10] Late presentations of up to 454 days have been reported in the literature.[11] Symptoms are nonspecific and may include dyspnea, chest pain, fatigue, myalgia, palpitations, syncope, dizziness, or altered mental status.
Diagnostics[6]	• Baseline electrocardiogram (ECG) and serum troponins[12] • Check for increased serum troponin • ECG to rule out an acute coronary syndrome • Echocardiogram • Cardiac MRI is diagnostic • Endomyocardial biopsy (gold standard)

Post-Diagnosis[12]	• 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[13]
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)[14] • In steroid refractory, infliximab or anti-thymocyte globulin as second-line therapy • Pericardial window for cardiac tamponade

References

1. Tajiri K, et al. ***Front Cardiovasc Med*** 2019;6:3.
2. Mahmood SS, et al. ***J Am Coll Cardiol*** 2018;71:1755-64.
3. Johnson DB, et al. ***N Engl J Med*** 2016;375:1749-55.
4. Moslehi JJ, et al. ***Lancet***. 2018;391:933.
5. Al-Kindi SG, et al. ***Lancet***. 2018;392:382-3.
6. Guo X, et al. ***Thorac Cancer***. 2020;11:475-80.
7. Topalian SL, et al. ***N Engl J Med***. 2012;366:2443-54.
8. Tawbi HA, et al. ***N Engl J Med***. 2018;379:722-30.
9. Larkin J, et al. ***N Engl J Med***. 2015;373:23-34.
10. Ganatra S, et al. ***Oncologist*** 2018;23:879-86.
11. Escudier M, et al. ***Circulation***. 2017;136:2085-7.
12. Brahmer JR, et al. ***J Clin Oncol***. 2018;35:1714-68.
13. Michel L, et al. ***Int J Cardiol Heart Vasc***. 2019;25:100420.
14. Ismail TF. ***Clin Med (Lond)***. 2020;20:48-51.