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VIEWPOINT

Cardiac Troponin I and T in ICI Myocarditis Screening, Diagnosis, and Prognosis

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Immune checkpoint inhibitors (ICIs) have become a key pillar in the oncology treatment landscape, with a growing number of indications for multiple cancers in both curative and palliative settings.[1] Their successful implementation is counterbalanced by the risk of immune-related adverse events. These span from mild and treatable, including low-grade thyroiditis, to acute and life-threatening, as in the case of fulminant ICI myocarditis. Patients who are successfully treated for ICI myocarditis are at high risk of recurrence if rechallenged with ICI therapy, but withholding these agents can lead to increased cancer-related morbidity and mortality. Therefore, early and accurate diagnosis of ICI myocarditis with precise risk stratification is of major clinical relevance.

Cardiac troponin (cTn) is the key circulating biomarker of myocardial injury and forms part of the definition of ischemic and nonischemic myocardial pathologies. Using the recommendations of the Task Force for the Universal Definition of Myocardial Infarction,[2] the diagnosis of myocardial injury (acute or chronic) is established when at least 1 cTn measurement is above the upper reference limit (URL), defined by the manufacturer as the 99th percentile for a healthy population free of known cardiovascular disease (CVD) and most risk factors. This definition applies to both cTn isoforms (cardiac troponin I [cTnI] and cardiac troponin T [cTnT]) and different generation cTn assays, including high-sensitivity (hs) cTnI and cTnT.

The International Cardio-Oncology Society consensus statement defines ICI myocarditis as a new cTn elevation with either positive cardiac magnetic resonance or with the presence of 2 minor clinical criteria.[3] Although elevations of cTnI and cTnT are both recognized as sensitive for the diagnosis of ICI myocarditis, a recent preference has been to use cTnI based on the reports of cTnT elevations in patients with immune-related myositis without cardiac involvement.[4,5] The concern for low specificity of the cTnT assay for myocarditis is relevant given the frequent overlap between ICI-related myositis, myasthenia gravis, and myocarditis.[1,6] In addition, clinical symptoms of myocarditis can be vague or even nonexistent, making the diagnosis heavily dependent on cTn changes. In clinical practice in the general population, cTnI and cTnT are both widely used for the diagnosis of acute myocardial infarction (AMI), and institutions commonly implement a single test (with regard to the cTn isoform, manufacturer, and generation/type) to standardize AMI protocols.

WHICH cTn TEST TO USE WHEN ICI MYOCARDITIS IS SUSPECTED?

Most ICI myocarditis studies used clinically available cTn assays, although recognizing that heterogeneous results have been reported between clinically approved cTnI assays with marked differences between different generations of assays, even between conventional and hs assays from the same manufacturer.[6] However, biologic differences between cTnT and cTnI constitute the most clinically significant distinction. Important observations come from a study by Lehmann et al,[7] who investigated serial cTn values in 60 patients hospitalized with ICI

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myocarditis. The authors observed a rapid rise and decline of cTnI compared to more prolonged and sustained cTnT elevations. They also found that a significant increase of cTnT to >32-fold above the URL was a strong predictor of major adverse cardiomyotoxic events with an HR of 11.[7] Although these results may seem to be at odds with the reports of low specificity and false-positive results of cTnT vs cTnI for ICI myocarditis diagnosis, a more in-depth look reveals striking similarities with what we know about the differences in cTnI and cTnT values and prognostic information in the general population and chronic disease states.[8]

In a direct comparison of 4 high-sensitivity cardiac troponin assays (1 high-sensitivity cardiac troponin T [hs-cTnT] and 3 high-sensitivity cardiac troponin I [hs-cTnI]) in 9,810 participants without known CVD in the National Health and Nutrition Examination Survey, hs-cTnT values above the URL were found in 3.1% compared to 0.6% to 0.9% for hs-cTnI.[9] A higher prevalence of hs-cTnT above the URL was described among additional cohorts of asymptomatic individuals and patients, including patients with cancer.[8,10] One explanation for these observations is that the current 99th percentile threshold for hs-cTnT, designed to "rule out" AMI, may inadvertently include patients with chronic subclinical myocardial injury caused by systemic disease, cancer, or cancer treatment among those with positive results. Possible mechanistic insight is offered by a recent report that demonstrated increased expression of *TNNT2*, the gene encoding cTnT, in muscle biopsies from patients with myopathies.[11] Together, these findings suggest that skeletal muscle may contribute to elevated cTnT in the absence of cardiac disease. The study by Lehmann et al[7] also found increased *TNNT2* (but not *TNNI3* encoding cTnI) expression in skeletal muscle of patients with myositis, further supporting this hypothesis.[6,7]

WHICH cTn SHOULD BE USED FOR PROGNOSIS IN PATIENTS WITH ICI MYOCARDITIS?

In the general population, modestly elevated levels of cTnI and cTnT are both associated with all-cause and CVD-specific mortality, whereas hs-cTnT elevations have stronger associations with heart failure and overall mortality compared to hs-cTnI.[8] At the present time, we lack large cohort data correlating cTnT or cTnI levels with major adverse cardiovascular events (MACE) in all patients receiving ICIs; this represents an important knowledge gap in cardio-oncology. In patients with an established diagnosis of ICI myocarditis, both elevated cTnT and elevated cTnI have been prognostic for MACE, with a caveat that cTn cutoff values and definitions of MACE have varied.[5,7,12] In the study by Lehmann et al,[7] a nonstandard approach was taken to include respiratory muscle failure requiring ventilatory support as part of the composite outcome of MACE. This change in the definition represents a challenge when comparing the performance of biomarkers with other studies that used traditionally accepted definitions of MACE as a cardiovascular outcome. Indeed, respiratory muscle failure occurred in 50% of patients with MACE, likely reflecting high morbidity in patients with concomitant skeletal myopathies. As a result, the excellent predictive value of cTnT reported in this study might have been caused in part by the inclusion of myositis as a major contributor to MACE[6,7] (**Figure 1**).

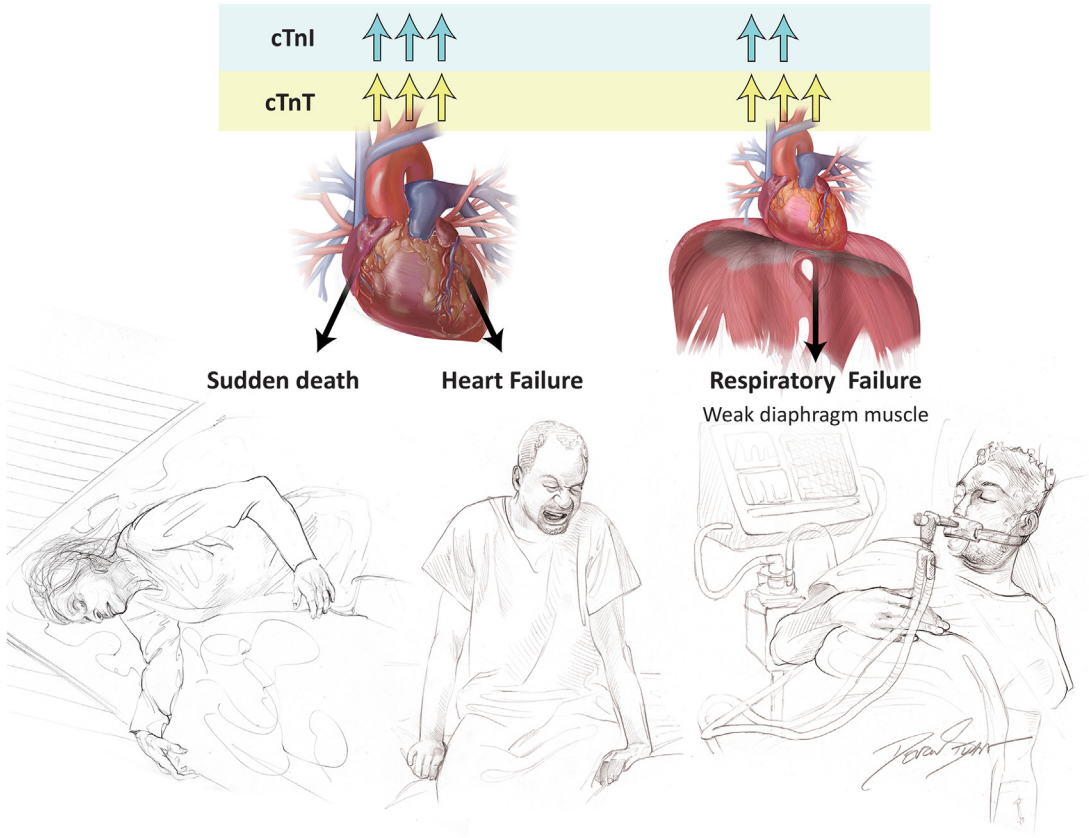
WHICH cTn TEST IS BETTER TO ASSESS DIFFERENTIAL DIAGNOSES?

An important consideration in the diagnosis of ICI myocarditis is the exclusion of AMI, which may have a similar clinical presentation, including elevated levels of cTns. In contrast to cTn distinctions in asymptomatic patients, there is a rapid and often logarithmic increase in cTnT and cTnI levels in patients with AMI, with high concordance and similar diagnostic performance characteristics between the 2 tests.[13] Indeed, in clinical practice, most providers will have access only to a single cTnI or cTnT assay that is chosen by their institution for AMI diagnosis and rule out. This is relevant for patients with cancer receiving ICIs who often may be at increased risk for both ischemic and nonischemic injury.[10] Recent reports have suggested the role of ICIs in the development and progression of atherosclerotic plaque,[14] thus amplifying the importance of excluding myocardial ischemia and using additional testing (such as cardiac magnetic resonance, coronary angiography, and/or endomyocardial biopsy) to establish an accurate diagnosis. Obtaining a baseline (pre-ICI) cTn value may mitigate the need for additional diagnostic tests in patients with acute symptoms, particularly when characterized with only mildly elevated cTn levels.

SHOULD WE SCREEN WITH cTn?

At the present time, cTn screening in asymptomatic patients receiving ICIs varies significantly in oncology practices. Serial cTn testing was investigated in a cohort of 214 patients receiving ICIs, 24 of whom had elevated hs-cTnI values during treatment, and of

FIGURE 1 **cTnI and cTnT Predict Major Adverse Events in ICI-Related Myocarditis**



In patients diagnosed with immune checkpoint inhibitor (ICI)-related myocarditis elevations in both cardiac troponins, cardiac troponin I (cTnI) and cardiac troponin T (cTnT) predict major adverse cardiovascular events. Elevated cTnI is associated with primary cardiovascular adverse events (eg, sudden cardiac death or heart failure), whereas elevations in cTnT are also predictive of myotoxic complications that involve myositis (respiratory failure caused by diaphragmatic muscle weakness).

those, only 3 were diagnosed with ICI myocarditis.[15] In this small sample, the positive predictive value of hs-cTnI was 12.5% at 55 ng/L and 100% at the 2,000-ng/L threshold,[15] indicating that more research is needed to determine who may benefit from routine testing during treatment. Although data are limited, we recommend establishing a baseline, pre-ICI initiation cTn value (using the locally available clinical cTn assay) to detect pre-existing chronic myocardial injury and to facilitate the interpretation of subsequent, symptom-based cTn testing. The potential downsides of this approach, such as delays in ICI initiation and inappropriate testing, can be overcome by developing and implementing a multidisciplinary immuno-oncology toxicity protocol. Chronic baseline elevations of cTn are likely to be common, particularly in the older population of patients with comorbidities, and should not trigger serial testing but rather inform the cardiovascular risk. When incorporated in a collaborative protocol with the oncology team, baseline cTn could offer an opportunity to optimize CVD and risk factor management without delaying ICI initiation.

In summary, cTn is a key clinical diagnostic test in patients receiving ICIs and presenting with suspected myocardial injury. The current evidence indicates that 1) information conveyed by elevated cTnI and cTnT measurements is likely complementary; 2) in the acute symptom setting, cTnT is a less specific marker of ICI myocarditis and may reveal the presence of myositis; 3) both the amplitude and rate of cTn increase together with the rate of decline (ie, typically accelerated in AMI) need to be considered; 4) precise and standardized definitions of MACE are critical to assess and compare diagnostic and prognostic accuracy; and 5) prospective data in large

cohorts of patients receiving ICIs are needed to determine the clinical utility of cTnT and cTnI screening and predicting MACE and overall outcomes.

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