Viewpoint

# Advances in Diagnosis and Treatment of Cancer Immunotherapy and CAR-T Cell–Related Myocarditis

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Modern cancer immunotherapy has revolutionized oncology, and its indications have expanded rapidly. Immune checkpoint inhibitors (ICI) activate the immune system, and they include monoclonal antibodies that block cytotoxic T lymphocyte antigen-4 (CTLA-4), programmed death receptor 1 (PD-1) and programmed death ligand-1, or lymphocyte activation gene 3, which act as "brakes" in the activation of T cells and immune cells. Responses are generally long-lasting and are optimized by combination therapy. However, the toxicities of these agents are caused by disruption of T-cell immune tolerance, manifesting as autoimmune events.[1] More recently, chimeric antigen receptor T cell (CAR-T cell) therapies have emerged as an innovative immunological treatment for patients suffering from advanced and refractory oncohematological neoplasms. Infusion of modified T cells, exposing chimeric receptors on the cell surface, leads to an immune response against tumor cells.

## Immune checkpoint inhibitors

The incidence of myocarditis in patients using ICI is low, around 1%. However, several series describe mortality between 30% and 40%. This is the primary reason that every effort is made for myocardial protection and early identification of signs of inflammatory response onset, in addition to understanding of T cell and macrophage stimulation and cytokine production.[2,3] The onset of the lesion is most frequently observed observed early after the first dose of immunotherapy with a median time to onset of 30 days, with an average resolution of 90 to 120 days.[4] Patients over 60 years of age are the most affected in the majority of series.[5]

## Keywords

Immunotherapy; Immune Checkpoint Inhibitors; Adoptive Immunotherapy; Myocarditis; Neoplasms

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Patients with suspected ICI-associated myocarditis may develop from asymptomatic conditions with increased biomarkers to severe presentations including cardiogenic shock, ventricular arrhythmias, and sudden death. Dyspnea and asthenia are the most common complaints related to ICI-associated myocarditis; chest pain may also occur.[6] The combination of ICI appears to be an important risk factor compared to monotherapy.[7]

For the diagnosis of ICI-associated myocarditis, electrocardiogram (ECG) and troponin are initial methods. Although it does not demonstrate a specific pattern, ECG is altered in approximately 90% of the cases. The presentation of arrhythmias after the initiation of ICI is highly suggestive and may include atrial and ventricular arrhythmias and atrioventricular blocks. Troponin is the most relevant biomarker in this context, and it has already been shown that its admission, peak, and discharge values are predictive of major events. Even in patients with a favorable course, troponin can remain elevated for weeks or months after the beginning of immunosuppressive therapy, which can be explained by the long half-life of ICI.[8] Due to the frequent association with myositis (30%), creatine phosphokinase test should be considered.[8] Likewise, the natriuretic peptides BNP and NT-proBNP (myocardial stress markers) may increase, and they have prognostic value when they remain at high levels in spite of treatment. The echocardiogram provides important information, especially regarding ventricular function. Nonetheless, half of patients may have normal ventricular function; accordingly, the use of more refined techniques, such as global longitudinal strain assessment, seems to add additional information for diagnosis and prognosis.[9] Cardiac magnetic resonance imaging (CMR) is the most used non-invasive technique for diagnosis of myocarditis, applying the modified Lake Louise criteria, including delayed enhancement techniques and T1 and T2 parametric maps; however, despite its high specificity, it has low sensitivity, with delayed enhancement being present in only 48% of cases, making it impossible to rule out diagnosis with a negative test.[10] Based on these limitations of non-invasive methods, endomyocardial biopsy plays an important role in confirming the diagnosis and should be considered in patients with suspected myocarditis due to ICI, especially when non-invasive tests do not establish the diagnosis; the infiltrate pattern involves lymphocytes (CD3) and macrophages (CD68) and,

when there is a high degree (above 50 cells/field), it has a prognostic role, suggesting a fulminant pattern[11] (Table 1 and Figure 1).

Treatment of myocarditis has been extrapolated from therapies for noncardiac toxicities associated with ICI, including cessation of ICI, supportive care, and corticosteroid therapy. Adverse events related to the immune system are usually treated with prednisone. In the case of myocarditis, higher doses of steroids (for example, intravenous methylprednisolone 1 g) have been advocated. In addition to corticosteroids, other immunosuppressive therapies primarily targeting T lymphocytes have been tested for ICI-related myocarditis in a small number of patients.[12] These therapies have included abatacept and Janus kinase inhibitors (tofacitinib and ruxolitinib). Nonetheless, it is understood that not all cases of ICI-associated myocarditis are similar, and there is a subgroup that does not require aggressive treatment. There are studies of prospective cohorts in patients with suspected myocarditis, based on asymptomatic increases in troponin and confirmed by endomyocardial biopsy, who did not receive or require initiation of immunosuppressive therapies and in some cases remained on immunotherapy with good clinical evolution.[13] These cases further highlight the clinical heterogeneity of ICI-associated myocarditis and the critical importance of establishing criteria to guide treatment. Furthermore, potential tumor growth after aggressive immunosuppression must be considered.[12] The main challenge is re-exposure. There are still no robust data to support this decision, and conduct must be individualized. It is recommended to consider, together with the oncologist, the therapeutic options available to the patient and the severity of the event that occurred.[12]

**Table 1 – Clinical and imaging findings for diagnosing ICI-associated myocarditis**

| | |
|---|---|
| Chest pain | 14% to 37% |
| Dyspnea/fatigue | 71% to 76% |
| Myasthenic-like syndrome | 11% to 30% |
| Altered ECG<br>Ventricular arrhythmia<br>Supraventricular arrhythmia<br>Conduction disorders<br>Cardiac arrest | 46% to 89%<br>< 27%<br>< 30%<br>< 17%<br>7% to 9% |
| Increased troponin | 46% to 94% |
| Increased natriuretic peptides | 65% to 100% |
| Cardiac magnetic resonance<br>Delayed enhancement<br>T2 mapping | <br>23% to 48%<br>26% |
| Echocardiogram<br>Reduced LVEF | <br>49% to 50% |
| Myositis | 23% to 30% |

*ECG: electrocardiogram; ICI: immune checkpoint inhibitors; LVEF: left ventricular ejection fraction. Adapted from Lehmann et al.[8]*

## CAR-T cell

Clinical trials of CAR-T cell therapy have reported low rates of cardiotoxicity, possibly due to patient selection. However, subsequent retrospective cohort studies have observed major adverse cardiovascular events in 10% to 20% of patients.[14]

Cardiac injury associated with CAR-T cell therapy is associated with the development of cytokine release

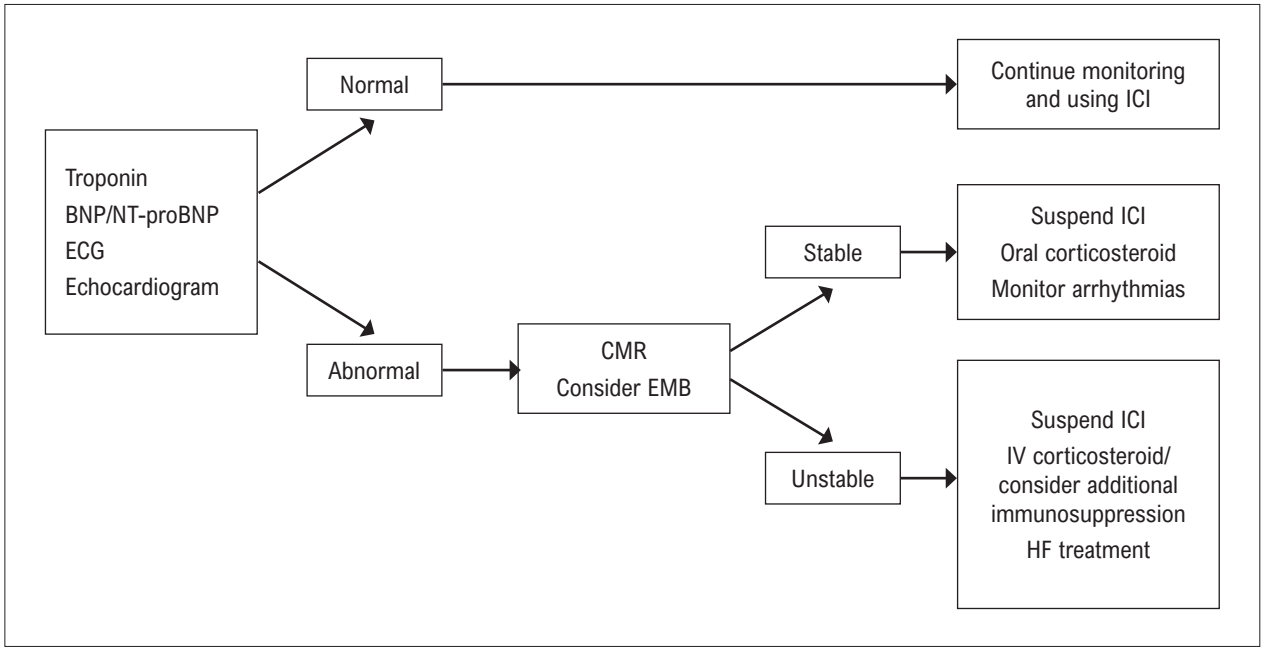


**Figure 1 –** *Flowchart for monitoring, diagnosing, and treating ICI-associated myocarditis. CMR: cardiac magnetic resonance imaging; ECG: electrocardiogram; EMB: endomyocardial biopsy; HF: heart failure ICI: immune checkpoint inhibitors; IV: intravenous. Adapted from Stein-Merlob et al.[1]*

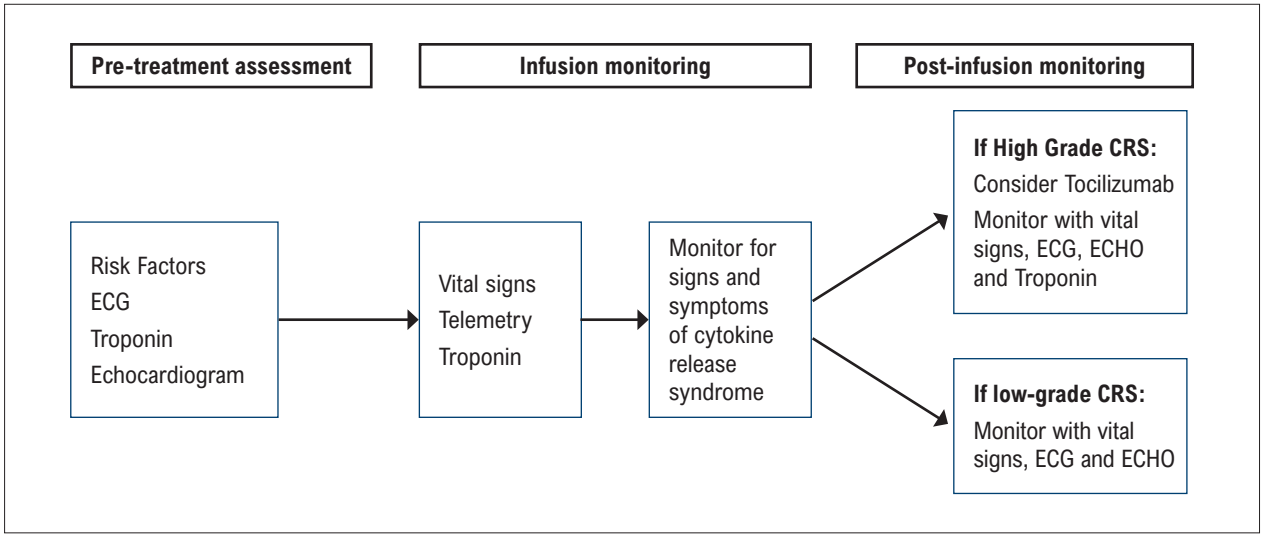


**Figure 2 –** *Flowchart for monitoring and treating CAR-T cell–associated cardiotoxicity. ECG: electrocardiogram; ECHO: echocardiogram; CRS: Cytokine release syndrome. Adapted from Camilli et al.[14]*

syndrome (CRS), and the signs and symptoms of cardiotoxicity include hypotension, tachycardia, arrhythmias (including atrial, ventricular, and prolonged QT), and symptoms of heart failure.[14]

Because patients with CRS grade ≥ 2 are more likely to develop cardiotoxicity, a general approach to managing CRS is applied with additional specific cardiac interventions as needed.[14] In addition to intravenous fluids, vasopressors, and oxygen supplementation as needed, the IL-6 antagonist tocilizumab should be considered for moderate to severe CRS. Repeated doses of these agents may be necessary, and steroids are recommended in cases that are refractory to IL-6 antagonists. Additionally, patients with grade 3 or 4 CRS should be transferred to intensive care for continued monitoring, control of arrhythmias and circulatory shock, and non-invasive positive pressure or mechanical ventilation as needed.[15] Figure 2 displays a flowchart of surveillance and treatment for CAR-T cell–related cardiotoxicity.

## Conclusion

The cardiac immune microenvironment is modified throughout cancer therapy, especially when using ICI/CAR-T cell therapy, proving to be more prone to disordered stimulation of T cells and macrophages. Thus, myocardial infiltration with lymphocytes and cytokines occurs. Questions regarding individual genetic predisposition remain an object of study and show a promising field in better understanding the predisposition and protection of patients undergoing immunotherapy.

## Author Contributions

Conception and design of the research, Acquisition of data, Writing of the manuscript and Critical revision of the manuscript for important intellectual content: Macedo AVS, Grippa A, Luz KRM, Nunes NCC, Mangini S.

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### Study association

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### Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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