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## **Clinical Features, Management, and Outcomes of Immune Checkpoint Inhibitor-Related Cardiotoxicity**

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Immune checkpoint inhibitors (ICIs) represent a major advance in the treatment of cancer. Although clinical trials reported a low incidence of immune-related cardiovascular adverse events,<sup>1</sup> the number of published life-threatening cases of cardiotoxicity is increasing.<sup>2</sup> In this descriptive observational analysis, we aimed to describe the clinical manifestations, management, and outcomes of patients who developed ICI-related cardiotoxicity.

The medical records of patients with a clinical suspicion of ICI-related cardiotoxicity were reviewed from the databases of 2 cardio-oncology units between March 2015 and April 2017. The patients are managed according to similar protocols. Because no specific follow-up had previously been established for patients receiving ICIs during the study period, the oncologists referred patients receiving ICIs only on the basis of their clinical suspicion of cardiovascular events. These patients had a standardized evaluation including clinical consultation, ECG, transthoracic echocardiography, and measurement of brain natriuretic peptide and troponin I serum levels. The management of cardiotoxicity was left to the physician's discretion. The study was approved by our institutional review board, and informed consent has been obtained from the subjects. To create a pooled analysis, we also searched PubMed for English articles reporting cases of ICI-related cardiotoxicity until April 2017. We selected the cases reporting in detail the patient characteristics and the disease evolution. Among the selected cases, we excluded those for which data were considered insufficient to formally conclude that clinical manifestations were related to ICIs.

A total of 30 patients with ICI-related cardiotoxicity were finally analyzed in this study, including 12 newly diagnosed patients in the 2 cardio-oncology unit and 24 patients with sufficient data previously reported in 10 case series. The data of those 24 patients were summarized in a recent review<sup>2</sup> and in 2 additional case reports.<sup>3,4</sup> The characteristics of the 30 patients are summarized in the Table. Cardiotoxicity was diagnosed at a median of 65 days (range, 2-454 days) after the initiation of ICIs and occurred after a median of 3 (range, 1-33) infusions. The rate of cardiotoxicity was higher after the first and third infusions, corresponding to the period after the first and third infusions. Dyspnea, palpitation, and signs of congestive heart failure were the most frequent clinical manifestations. Left ventricular systolic dysfunction was reported in 79% of patients, and Takotsubo syndrome-like appearance occurred in 14%. Atrial fibrillation, ventricular arrhythmia, and conduction disorders were observed in 30%, 27%, and 17% of patients, respectively. They were isolated (without left ventricular systolic dysfunction) in 3%, 7%, and 13% of patients, respectively. Concomitant signs of myositis were present in 23% of patients. Of the 18 patients with available data on left ventricular ejection fraction evolution, complete reversibility of left ventricular systolic dysfunction was significantly associated with corticosteroid therapy (8 of 12 [67%] versus 1 of 6 [17%];  $P=0.04$ ). Eight patients (27%) died of cardiovascular complications. The causes of death were refractory ventricular arrhythmia ( $n=3$ ), heart failure ( $n=2$ ), pulmonary embolism ( $n=1$ ), sudden death ( $n=1$ ), and cardiac arrest after the diagnosis of a conductive disorder ( $n=1$ ). Cardiovascular mortality was significantly associated with conduction abnormalities (80% versus 16%;  $P=0.003$ ) and ipilimumab-nivolumab combination therapy (57% versus 17%;  $P=0.04$ ). Immune therapy was administered again after the first episode of cardiotoxicity only in the 4 patients (14%) without any recurrences.

The mechanisms of ICI-related cardiovascular events remain not well known, but this study provides a more comprehensive clinical description of this cardiotoxicity by analyzing a greater number of patients compared with previous studies. It shows that clinical manifestations are variable and associated with high cardiovascular mortality. Although we observed a higher incidence rate of cardiotoxicity during the first and third months of treatment, clinicians should keep in mind that cardiotoxicity can develop at any time; in our study, the interval varied from 2 to 454 days. Therefore, a comprehensive cardiac evaluation might be justified not only before the beginning of ICI therapy (as a reference) but also in cases of cardiovascular manifestations during treatment and systematically at the third month or after the third infusion. However, further data are needed to determine which cardiovascular investigations are relevant in this situation. In our analysis, cardiovascular mortality was high and significantly associated with the occurrence of conduction disorders. Although guidelines recommend a definite discontinuation of immune therapy in cases of life-threatening and severe adverse events,<sup>5</sup> the management of each case should be individualized according to cancer status and the presence of toxicity regression. Indeed, corticosteroid use was associated with a higher probability of left ventricular function recovery, and no recurrence of cardiotoxicity was observed in the patients who underwent ICI readministration. This study has several limitations, including retrospective design, small sample size, and reporting bias.

In conclusion, this work provides new insights into the cardiotoxicity observed in patients treated with ICIs. Because the number of patients exposed to this new immune therapy is expected to dramatically increase in the near future, our study encourages further work to define guidelines for cardiovascular monitoring and management.

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**Table**

	Patients With Available Data, n	Value
Age, median (minimum–maximum), y	30	72 (23–88)
Male, n (%)	30	23 (77)
Previous cardiovascular disease, n (%)	30	15 (50)
Cancer, n (%)		
Melanoma	30	23 (77)
NSCLC	30	4 (13)
Others	30	3 (10)
ICIs, n (%)		
Ipilimumab	30	11 (37)
Nivolumab	30	10 (33)
Ipilimumab+nivolumab	30	7 (23)
Pembrolizumab	30	3 (10)
Atezolizumab	30	1 (3)
Type of cardiotoxicity, n (%)		
LVSD	29	23 (79)
Takotsubo syndrome–like appearance	29	4 (14)
Atrial fibrillation	30	9 (30)
Ventricular arrhythmia	30	8 (27)
Conduction abnormalities	30	5 (17)
Pericardial effusion	29	2 (7)
Time after initiation of ICIs, median (minimum–maximum), d	29	65 (2–454)
Infusions before ICIs, median (minimum–maximum), n	27	3 (1–33)
Initial clinical cardiovascular manifestations		
Dyspnea, n (%)	29	22 (76)
Palpitation, n (%)	29	4 (14)
Chest pain, n (%)	29	4 (14)
Heart failure, n (%)	29	24 (83)
Cardiac arrest, n (%)	29	2 (7)
ST-segment/T-wave abnormalities, n (%)	28	11 (39)
LVEF, median (minimum–maximum), %	26	35 (15–73)
LVEF ≤35%, n (%)	26	12 (46)
MRI, n (%)		
LGE	13	3 (23)
Myocardial edema	15	5 (33)
BNP or NT–pro-BNP elevation	14	14 (100)
Troponin elevation	26	12 (46)
Lymphocyte infiltration (histology)	9	8 (89)
Corticosteroids	30	21 (70)
LVSD completely reversible	18	9 (50)
Death resulting from cardiovascular causes	30	8 (27)

BNP indicates brain natriuretic peptide; ICI, immune checkpoint inhibitor; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; LVSD, left ventricular systolic dysfunction; MRI, magnetic resonance imaging; NSCLC, non-small cell lung cancer; and NT–pro-BNP, N-terminal probrain natriuretic peptide.