Cardiotoxicity caused by chemotherapeutics such as anthracyclines is well recognized. In recent years, immunotherapy has been successfully introduced in cancer treatment. Unfortunately, cardiotoxicity seems to have emerged as an issue in recent reports.1

STIMULATING ANTITUMORAL IMMUNE RESPONSES

For decades, immunologists and oncologists have attempted to stimulate antitumor immune responses to fight cancer. Initial attempts displayed marginal success because several inhibitory pathways such as cytotoxic T lymphocyte–associated protein 4 (CTLA-4), programmed cell death protein 1 (PD-1), and programmed cell death ligand 1 (PD-L1) dampen the antitumor functions of T lymphocytes. Tumors exploit these pathways to escape T cell–mediated tumor-specific immunity. Monoclonal antibodies targeting CTLA-4 (ipilimumab), PD-1 (nivolumab and pembrolizumab), and PD-L1 (atezolizumab, avelumab, durvalumab), called immune checkpoint inhibitors (ICIs), have revolutionized cancer treatments. However, dramatic responses are currently confined to few patients, presumably because of the complex network of immunosuppressive pathways in tumor microenvironments. Combined anti–CTLA-4 and anti–PD-1 blockade further enhances antitumor activity (Figure, A). ICIs are being tested in HIV-infected patients, characterized by overexpression of immune checkpoints and T-cell exhaustion.

IMMUNE-RELATED ADVERSE EVENTS ASSOCIATED WITH CHECKPOINT INHIBITORS

As a result of the role played by immune checkpoints in the maintenance of self-tolerance, their therapeutic blockade can cause immune-related adverse events (IRAEs). IRAEs associated with ipilimumab were already evident in phase I studies. IRAEs are common, usually reversible, and not severe in most patients.1,2 PD-1 and PD-L1–blocking agents display different IRAEs (eg, renal and endocrine effects and cardiomyopathy) that resemble the autoimmune manifestations of PD-1–deficient mice.3 IRAEs associated with the ipilimumab/nivolumab combination require discontinuation of therapy in nearly 40% of patients. It is unclear whether the use of immunosuppressive agents (eg, tumor necrosis factor-α inhibitors) is more appropriate than high-dose glucocorticoids in the treatment of severe IRAEs.

CARDIOTOXICITY OF CHECKPOINT INHIBITORS IN PATIENTS WITH CANCER

The majority of studies on ICIs have underestimated cardiotoxicity3; however, occasional cases have been reported. Two cases of fulminant myocarditis after...
treatment with ipilimumab plus nivolumab for melanoma have been recently described. Both patients died after receiving the first doses despite intensive treatment. Hypertension was their only cardiovascular risk factor. Histological analysis demonstrated lymphocytic infiltrates within the myocardium, the cardiac sinus, and the atrioventricular nodes. This observation can explain the complete heart block that can occur in these patients. PD-L1 was expressed on injured cardiomyocytes and on infiltrating CD8+ T cells (Figure, B). Overexpression of PD-L1 on the injured myocardial cell is consistent with the constitutive expression of PD-L1 in human hearts and its upregulation in T cell–mediated myocarditis in mice. Johnson et al also assessed the frequency of myocarditis and myositis in the safety databases of Bristol-Myers Squibb to identify the occurrence of these events in patients treated with nivolumab, ipilimumab, or both. Among 20 594 patients treated with these ICIs, 18 drug-related myocarditis cases (0.09%) were reported. Patients who received combination therapy (nivolumab plus ipilimumab) had more severe and frequent myocarditis than those who received nivolumab alone (0.27% versus 0.06%). Myocarditis was diagnosed at a median of 17 days after the first treatment, suggesting the presence of early cardiotoxicity. Finally, severe and even fatal cardiovascular events have occurred, making analysis of the incidence of cardiotoxicity of ICIs a priority.

**MOVING FORWARD: THE INTEGRATION OF CARDIO-ONCOLOGY AND IMMUNOLOGY**

Cardiologists and oncologists should be aware of immune-mediated myocarditis because of its fulminant nature.
conversion of myocarditis into lethal disease, suggesting that PD-1/PD-L1 and CTLA-4 play important roles in limiting T cell–mediated autoimmune myocarditis. Moreover, isolated ischemic-reperfused rat hearts showed increased expression of PD-1 and PD-L1 in cardiomyocytes. Myocarditis has a wide spectrum of presentations reflecting the many causes and the variable pattern of tissue involvement. Moreover, patients with autoimmunity can have subclinical or subacute myocarditis. At present, exclusion criteria related to preexisting autoimmune diseases in patients with cancer treated with ICIs are based on personal experience, but patients with autoimmune disorders are usually excluded from trials with ICIs. Approximately 14% of patients with lung cancer have a concurrent diagnosis of autoimmune disease, indicating that autoimmunity needs to be considered before the initiation of these therapies. Menezes and collaborators reported their experience with 2 groups of patients with preexisting autoimmune disease and melanoma treated with ipilimumab or anti–PD-1. Although 20% to 30% of these patients experienced an autoimmune flare, the authors concluded that treatment with either ipilimumab or anti–PD-1 is feasible for patients with certain preexisting autoimmunities. Given the heterogeneity and the wide spectrum of severity of autoimmune disorders, specific guidelines for exclusion criteria and treatment are needed. Similarly, there are no validated guidelines for the treatment of myocarditis in the setting of cancer immunotherapy. Wang and collaborators proposed an algorithm that represents an excellent basis for a consensus guideline.

Newer monoclonal antibodies targeting different immune checkpoints and a new generation of cancer therapies (eg, engineered T cells and cancer vaccines), beyond ICIs, are under development for several tumors. Therefore, cardiovascular evaluation appears necessary to detect the potential cardiotoxicity of newer cancer immunotherapies (Table) because these agents are often used in combination with cardiotoxic kinase inhibitors.

All cases of cardiotoxicity associated with ICIs reported so far occurred immediately after the infusion or during the first year of therapy, but prospective studies should assess whether late-onset chronic cardiotoxicity can occur.

Constitutive expression of PD-1 and PD-L1 in human and murine myocytes and the recent identification of PD-L1 on injured myocytes in patients with fulminant myocarditis treated with checkpoint inhibitors suggest that cytokines and immune cells can upregulate PD-1/PD-L1 pathways in the human myocardium (Figure, C). Additional in vitro and in vivo research is needed to further understand the mechanisms of these cardiotoxicities (Table).

With a growing number of patients treated immune ICIs, a tight collaboration among cardiologists, oncologists, and immunologists appears necessary for better management of ICI cardiotoxicity.

**Table. What is Known and What Needs to Be Done About Cardiotoxicity of Checkpoint Inhibitors in Cancer**

<table>
<thead>
<tr>
<th>What Is Known</th>
<th>What Needs to Be Done</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monoclonal antibodies targeting immune checkpoints on T lymphocytes (eg, anti-CTLA-4, anti–PD-1, and anti–PD-L1) are increasingly used in the management of solid and hematologic malignancies</td>
<td>To assess the real incidence of early and late cardiac toxicity associated with ICIs, alone and in combination</td>
</tr>
<tr>
<td>ICIs can give rise to autoimmune side effects called IRAEs</td>
<td>To evaluate whether ICIs exacerbate subclinical/subacute myocarditis in patients with systemic autoimmune disorders</td>
</tr>
<tr>
<td>Some IRAEs resemble autoimmune manifestations seen in CTLA-4– and PD-1–deficient animals</td>
<td>To construct collaborative (cardiologists, oncologists, immunologists) guidelines for the prevention and treatment of cardiac toxicity associated with ICIs that need to be driven by data obtained through clinical trials or large registries</td>
</tr>
<tr>
<td>Experimental PD-1 and CTLA-4 deficiency can cause autoimmune myocarditis</td>
<td>To construct collaborative (cardiologists, oncologists, immunologists) guidelines for the prevention and treatment of cardiac toxicity associated with ICIs, alone and in combination</td>
</tr>
<tr>
<td>More than 200 clinical trials are ongoing to evaluate the safety and efficacy of different ICIs in patients with solid and hematologic tumors</td>
<td>Ongoing and future clinical trials to collect cardiac and cardiovascular data points and prospective data on cardiovascular risk and outcomes, especially in potentially high-risk patients</td>
</tr>
<tr>
<td>PD-1 and PD-L1 are constitutively expressed in murine and human myocytes, and their expression can be increased during myocarditis and myocardial ischemia</td>
<td>Experimental research (eg, gut microbiota) to understand the mechanisms underlying cardiac toxicity caused by ICIs, alone and in combination</td>
</tr>
<tr>
<td>Autoimmune myocarditis rarely occurs in patients with cancer treated with ICIs used as single agents</td>
<td>Clinical investigation to understand the mechanisms underlying cardiac toxicity caused by different ICIs, alone and in combination, in various types of cancer</td>
</tr>
<tr>
<td>Cardiac complications are more frequent with combined ICIs</td>
<td>To identify biomarkers of early and late cardiac toxicity caused by ICIs</td>
</tr>
</tbody>
</table>

CTLA-4 indicates cytotoxic T lymphocyte–associated protein 4; ICIs, immune checkpoint inhibitors; IRAE, immune-related adverse event; PD-1, programmed cell death protein 1; and PD-L1, programmed cell death ligand 1.

**ACKNOWLEDGMENTS**

The authors thank Prof. Gianni Marone, MD, for his invaluable intellectual suggestions, Fabrizio Fiorbianco for preparing the Figure, and Gjada Criscuolo for excellent secretarial help.
SOURCES OF FUNDING
This work was supported in part by grants from Regione Campania Center for Basic and Clinical Immunology Research Laboratory, CRÈME Project, TIMING Project, and University of Naples Federico II.

DISCLOSURES
Dr Tocchetti received speaker fees from Alere. The other authors report no conflicts.

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FOOTNOTES
Circulation is available at http://circ.ahajournals.org.

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Cardiac Toxicity of Immune Checkpoint Inhibitors: Cardio-Oncology Meets Immunology
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doi: 10.1161/CIRCULATIONAHA.117.029626
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2017 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

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