Cardiac Toxicity of Immune Checkpoint Inhibitors

Cardio-Oncology Meets Immunology

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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 cardiotoxicity[3]; however, occasional cases have been reported. Two cases of fulminant myocarditis after

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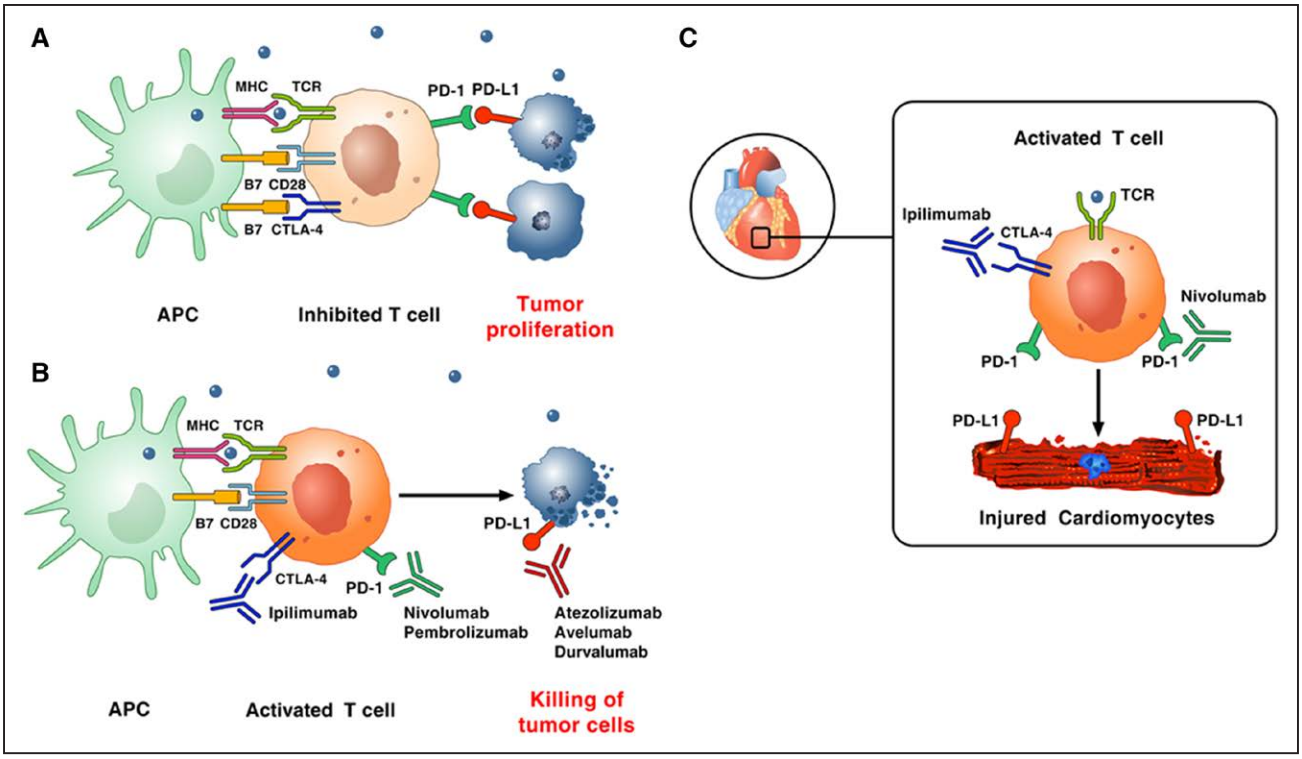

Figure. Mechanism of action of checkpoint inhibitors.
A, Tumor cells escape immune surveillance by promoting checkpoint activation. Tumor cells express the immune checkpoint activator programmed cell death ligand 1 (PD-L1) and produce antigens (blue dots) that are captured by antigen-presenting cells (APCs). These cells present antigens to cytotoxic $CD8^+$ T cells through the interaction of major histocompatibility complex (MHC) molecules and T-cell receptor (TCR). T-cell activation requires costimulatory signals mediated by the interaction between B7 and CD28. Inhibitory signals from cytotoxic T lymphocyte–associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1) checkpoints dampen T-cell response and promote tumor proliferation. **B**, Checkpoint inhibitors stimulate T-cell activation. Monoclonal antibodies targeting CTLA-4 (ipilimumab), PD-1 (nivolumab, pembrolizumab), and PD-L1 (atezolizumab, avelumab, durvalumab) block immune inhibitory checkpoints (CTLA-4, PD-1, and PD-L1, respectively) and restore antitumor immune response, resulting in tumor cell death via release of cytolytic molecules (eg, tumor necrosis factor-α, granzyme B, interferon-γ). **C**, Hypothetical mechanism by which checkpoint inhibitors can promote autoimmune lymphocytic myocarditis. PD-L1 is expressed in human and murine cardiomyocytes, and its expression can increase during myocardial injury. Combination of checkpoint blockade (ipilimumab plus nivolumab) unleashes immune responses and can cause autoimmune lymphocytic myocarditis. Lymphocytes in myocardium and tumors showed clonality of TCR, suggesting that heart and tumors can share antigens (blue dot) recognized by the same T-cell clones.

treatment with ipilimumab plus nivolumab for melanoma have been recently described.[3] 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.[4] Johnson et al[3] 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%).[3] 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

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progression.[3] The development of myocarditis in patients treated with ICIs has biological plausibility. Deletion of CTLA-4 and PD-1 axes can cause autoimmune myocarditis and dilated cardiomyopathy,[4] suggesting that these molecules play a role in the prevention of autoimmunity. In addition, genetic deletion of PD-L1, as well as treatment with anti–PD-L1, can transform transient 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,[1,5] 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. Menzies and collaborators[5] 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[1] 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,[3,5] 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[3,4] 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

What Is Known	What Needs to Be Done
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	To assess the real incidence of early and late cardiac toxicity associated with ICIs, alone and in combination
ICIs can give rise to autoimmune side effects called IRAEs	To evaluate whether ICIs exacerbate subclinical/subacute myocarditis in patients with systemic autoimmune disorders
Some IRAEs resemble autoimmune manifestations seen in CTLA-4– and PD-1–deficient animals	To construct collaborative (cardiologists, oncologists, immunologists) guidelines for exclusion criteria (eg, cardiovascular and autoimmune disorders) for patients undergoing cancer immunotherapy
Experimental PD-1 and CTLA-4 deficiency can cause autoimmune myocarditis	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
More than 200 clinical trials are ongoing to evaluate the safety and efficacy of different ICIs in patients with solid and hematologic tumors	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
PD-1 and PD-L1 are constitutively expressed in murine and human myocytes, and their expression can be increased during myocarditis and myocardial ischemia	Experimental research (eg, gut microbiota) to understand the mechanisms underlying cardiac toxicity caused by ICIs, alone and in combination
Autoimmune myocarditis rarely occurs in patients with cancer treated with ICIs used as single agents	Clinical investigation to understand the mechanisms underlying cardiac toxicity caused by different ICIs, alone and in combination, in various types of cancer
Cardiac complications are more frequent with combined ICIs	To identify biomarkers of early and late cardiac toxicity caused by ICIs

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.

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FOOTNOTES

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