




Cardiovascular Toxicity of Immune Checkpoint Inhibitors: Clinical Risk Factors

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Abstract

Purpose of Review Immune checkpoint inhibitors, such as monoclonal antibodies targeting CTLA-4, PD-1, and PD-L1, have improved the outcome of many malignancies, but serious immune-related cardiovascular adverse events have been observed. Patients' risk factors for these toxicities are currently being investigated.

Recent Findings Interfering with the CTLA-4 and PD-1 axes can bring to several immune-related adverse events, including cardiotoxic events such as autoimmune myocarditis, pericarditis, and vasculitis, suggesting that these molecules play an important role in preventing autoimmunity.

Summary Risk factors (such as pre-existing cardiovascular conditions, previous and concomitant cardiotoxic treatments, underlying autoimmune diseases, tumor-related factors, simultaneous immune-related toxic effects, and genetic factors) should be always recognized for the correct management of these toxicities.

Keywords Immune checkpoint inhibitors · Cardio-immuno-oncology · Cardiotoxicity · Risk factors

Introduction

Over the past decade, cancer therapy has been revolutionized by the development of immunotherapy [1]. Various types of immunotherapies have been developed; in particular, immune checkpoint inhibitors (ICIs) have dramatically changed the outcome for many groups of patients with advanced cancer

[2]. Indeed, for decades, oncologists have been developing strategies to modulate inflammation in order to achieve therapeutic anticancer immune responses [3, 4]. The first attempts were not really successful since cancer escapes T cell-mediated cancer-specific immunity via inhibitory pathways mediated by cytotoxic T lymphocyte-associated protein 4 (CTLA-4), programmed cell death protein 1 (PD-1), and programmed cell death ligand 1 (PD-L1) (all depressing the antineoplastic activity of T lymphocytes). On the opposite, in the last years, ICIs, such as monoclonal antibodies (mAbs) targeting CTLA-4, PD-1, and PD-L1, have improved the outcome of many malignancies, but serious immune-related cardiovascular adverse events have been observed [5•, 6•, 7]. Interfering with the CTLA-4 and PD-1 axes can result in autoimmune myocarditis and dilated cardiomyopathy [8•], suggesting that these molecules play an important role in preventing autoimmunity [9] (Fig. 1). Inhibitors of CTLA-4 include ipilimumab; inhibitors of PD-1 include nivolumab, pembrolizumab, and cemiplimab; and inhibitors of PD-L1 include atezolizumab, avelumab, and durvalumab (<https://www.fda.gov/drugs/resources-information-approved-drugs/hematologyoncology-cancer-approvals-safety-notifications>). These ICIs can also be used in combination (e.g., ipilimumab

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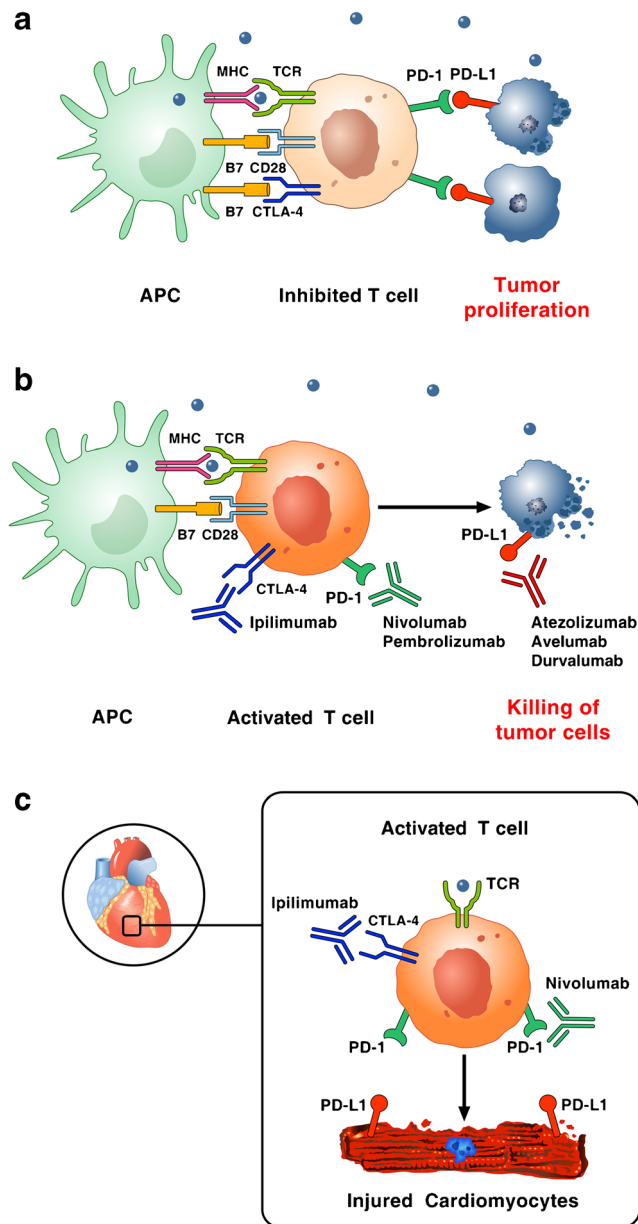


Fig. 1 Reproduced with permission from [9]. **a** Tumor cells escape immune surveillance by promoting checkpoint activation. Tumor cells express the immune checkpoint activator PD-L1 and produce antigens (blue dots) that are captured by antigen presenting cells (APCs). These cells present antigens to cytotoxic CD8⁺ T cells through the interaction of major histocompatibility complex (MHC) molecules and T-cell receptor (TCR). T-cell activation requires co-stimulatory signals mediated by the interaction between B7 and CD28. Inhibitory signals from CTLA-4 and 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 anti-tumor immune response, resulting in tumor cell death via release of cytolytic molecules (e.g., TNF- α , Granzyme B, IFN- 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. Importantly, 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

[5•, 16] (Table 1). Unfortunately, if on the one hand the activation of the immune system can determine the regression of serious tumors in some patients, on the other hand it can determine the appearance of immune-related adverse events (irAEs) [17, 18]. These immune-mediated toxicities occur among 70–90% of patients treated with ICIs [17] and include hepatitis, colitis, thyroiditis, pneumonitis, myositis, dermatitis, and hypophysitis [19]. They are typically reversible and can usually be controlled with glucocorticoid therapy [20]. ICI treatments have been also shown to lead to cardiovascular adverse reactions (CTX); immune-mediated CTX has been observed in individual cases with different presentations [6••]. In this manuscript, we describe risk factors and clinical manifestations of these cardiotoxicities.

Myocarditis

The incidence of ICI-associated myocarditis has been estimated to be between 0.27 and 1.14% in retrospective studies. [21••, 22••]

ICI-associated myocarditis can look like classic myocarditis, and the clinical presentations include signs of acute heart failure (chest pain, shortness of breath, pulmonary edema, and even cardiogenic shock), but can also present with arrhythmias, including heart blocks and both atrial and ventricular arrhythmias that can lead to syncope and sudden death [22••, 23]. In some cases, myocarditis can also be asymptomatic with mild degrees of ventricular dysfunction [24].

Most cases of ICI-associated myocarditis appear early, with a median time of 30 days of toxicity, which corresponds

plus nivolumab) in order to increase anticancer activity or can be combined with other cancer therapies [10].

Other immune checkpoints are represented by T-cell immunoglobulin and mucin-containing protein 3 (TIM-3) [11], lymphocyte-activated gene-3 (LAG-3) [12], T-cell immunoreceptor with Ig and ITIM domains (TIGIT) [13], B and T lymphocyte attenuator (BTLA) [14], and V domain Ig suppressor of T-cell activation (VISTA, also known as PD-1 homolog, or PD-1H) [15] and are currently being investigated for their therapeutic potential.

ICIs are now being used for the treatment of advanced metastatic cancers, including melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma, head and neck squamous cell carcinoma, urothelial cancer, refractory Hodgkin's lymphoma, and malignancies with microsatellite instability

Table 1 U.S. FDA–approved immune-checkpoint inhibitors for cancer [5••, 16]

Checkpoint	Checkpoint inhibitor	Approved uses
CTLA-4	Ipilimumab (Yervoy®)	Unresectable or metastatic melanoma, alone or combined to ipilimumab, or as adjuvant
		Advanced or metastatic renal cell carcinoma, combined to nivolumab
PD-1	Nivolumab (Opdivo®)	Microsatellite instability-high or mismatch repair–deficient metastatic colorectal cancer alone or combined to nivolumab
		Hepatocellular carcinoma (refractory) in combination with nivolumab
		Squamous NSCLC (metastatic)
		Unresectable or metastatic melanoma, alone or combined to ipilimumab, or as adjuvant
		Metastatic squamous NSCLC
		Small cell lung cancer (advanced or metastatic)
		Advanced renal cell carcinoma
		Relapsed classical Hodgkin’s lymphoma
		Recurrent or metastatic head-and-neck squamous cell carcinoma
		Advanced or metastatic urothelial carcinoma
PD-1	Pembrolizumab (Keytruda®)	Microsatellite instability-high or mismatch repair–deficient metastatic colorectal cancer alone or combined to ipilimumab
		Refractory or hepatocellular carcinoma
		Advanced or metastatic renal cell carcinoma alone or combined to ipilimumab
		Esophageal squamous cell carcinoma (advanced or metastatic)
		Unresectable or metastatic melanoma
		Metastatic NSCLC
		Small cell lung cancer (advanced or metastatic)
		Recurrent or metastatic head or neck squamous cell carcinoma
		Refractory classical Hodgkin’s lymphoma
		Locally advanced or metastatic urothelial carcinoma
PD-L1	Cemiplimab (Libtayo®)	Microsatellite instability-high or mismatch repair–deficient solid tumors and colorectal cancer
		Locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma
		Recurrent or metastatic cervical cancer
		Refractory primary mediastinal large B-cell lymphoma
		Hepatocellular carcinoma
		Recurrent or metastatic Merkel cell carcinoma
		Renal cell carcinoma (advanced or metastatic)
		Cutaneous squamous cell carcinoma (metastatic)
		Metastatic cutaneous squamous cell carcinoma
		Locally advanced or metastatic urothelial carcinoma
PD-L1	Atezolizumab (Tecentriq®)	Metastatic NSCLC
		Extensive-stage SCLC (ES-SCLC)
		Triple-negative breast cancer (TNBC)
		Hepatocellular carcinoma (unresectable or metastatic)
PD-L1	Avelumab (Bavencio®)	Metastatic Merkel cell carcinoma
		Locally advanced or metastatic urothelial carcinoma
PD-L1	Durvalumab (Imfinzi®)	Locally advanced or metastatic urothelial carcinoma
		Unresectable stage III NSCLC
		Extensive-stage SCLC (ES-SCLC)
Checkpoints under investigation and that have not undergone FDA approval		
TIM-3, LAG-3, TIGIT, BTLA, VISTA (PD-1H)		
CTLA-4, cytotoxic T lymphocyte-associated protein-4; PD-1, programmed cell death protein-1; PD-L1, programmed cell death 1 ligand-1; TIM-3, T-cell immunoglobulin and mucin containing protein 3; LAG-3, lymphocyte-activated gene-3; TIGIT, T-cell immunoreceptor with Ig and ITIM domains; BTLA, B- and T-lymphocyte attenuator; VISTA, also known as PD-1 homolog, or PD-1H, V domain Ig suppressor of T-cell activation. Approved indications are up to date as of July 2020		

approximately to the first or second administration of ICIs [25••].

The seminal paper from Mahmood and collaborators [22••] showed that pre-existing cardiovascular risk factors and disease are common in patients on ICIs (both in cases of myocarditis and in controls without myocarditis) [6••].

Combination ICI therapy (e.g., a CTLA-4 inhibitor combined with a PD-1 inhibitor) is the predominant risk factor for ICI-associated myocarditis [21••]. Moreover, myocarditis due to combination ICI therapy is also more severe than the one related to ICI monotherapy [21••]. There appears to be no correlation between ICI-associated myocarditis and age since

this complication seems to occur in a broad age range (20–90 years) [7, 22••, 25••, 26]. Toxicity reports show a possible predominance of this adverse reaction in males, but this does not indicate a predisposition of male compared to female sex, given that males are more represented in both ICI use and clinical trial enrollment [25••]. Other risk factors, theoretically, include other treatments (e.g., use of other cardiotoxic anti-neoplastic agents such as anthracyclines, anti-ErbB2 drugs, Raf and MEK inhibitors, and VEGF tyrosine kinase inhibitors) [27], underlying autoimmune diseases (e.g., rheumatoid arthritis, lupus erythematosus, sarcoidosis), tumor-related factors (cardiac antigens expressed in tumor, activation of T-cell clones against cardiac antigens), simultaneous immune-related toxic effects (ICI-related skeletal myositis), and genetic factors (gene polymorphisms of CTLA-4, PD-1, or PDL-1) [6••]. Recent observations also report a protective role for flu vaccination (FV) in the development of ICIs myocarditis and major adverse cardiac events (MACE). In particular, subjects who presented with ICI myocarditis had lower rates of FV. FV was also associated with a lower rate of ICI-related pneumonitis, and myocarditis cases had lower troponin levels and lower rates of cumulative MACE at follow-up in the FV population [28].

Laboratory tests and instrumental examinations are useful for the diagnosis of myocarditis and may reveal patients at higher risk. All diagnostic tests should be used wisely and guided by clinical reasoning. Markers of myonecrosis, including cardiac troponin (cTn), CK-MB (creatin kinase-muscle/brain), or total CK (creatin kinase), are useful for the diagnosis of myocarditis. In particular, it has been seen that troponin is the preferred biomarker, and since troponin T may also be elevated because of myositis, troponin I is preferred for establishing cardiac injury [29]. Interestingly, a discharge cardiac troponin T of more than 1.5 ng/mL has been reported to be associated with a fourfold increased risk of a major adverse cardiovascular event [22••]. Natriuretic peptides (B-type natriuretic peptide and NT-proBNP) may be elevated in patients with left ventricular dysfunction and heart failure and are frequently elevated in ICI-associated myocarditis [30]. However, BNP is not very specific because it can be chronically elevated in many cancer patients due to cancer-related inflammation [31] and to cancer progression and severity, suggesting the presence of subclinical functional and morphological heart damage in cancer patients [32].

Patients with conduction disease due to ICI therapy in the absence of generalized myocarditis tend to develop a potentially severe ICI-mediated sudden death. This evidence supports the importance of routine ECG monitoring with associated detailed evaluations (e.g., cardio-oncology referral for clinical assessment, cardiac imaging, and 48-h Holter ECG monitoring) of patients on ICI therapy presenting with palpitations, presyncope, or syncope. The ECG may show several changes, including intraventricular conduction delay, PR

interval prolongation, various forms of arrhythmias, and eventually complete heart block [21••, 7]. Therefore, ECG is neither sensitive nor specific enough for myocarditis screening.

Traditional echocardiography is also not specific for myocarditis and loses sensitivity in case of preserved systolic function [33, 34]. On the opposite, a recent study compared echocardiographic global longitudinal strain (GLS) in patients receiving ICI who had myocarditis and in patients receiving ICI without myocarditis. The authors showed that GLS decreases in patients with ICI myocarditis and is lower than in patients with ICI without myocarditis. Interestingly, GLS is lower in patients with ICI myocarditis presenting with both a preserved and reduced ejection fraction (EF). Importantly, the study also showed that, during follow-up, patients presenting with low GLS have a higher risk for major adverse cardiac events (MACE), including cardiovascular death, cardiogenic shock, cardiac arrest, and hemodynamically significant complete heart block [35•].

Cardiac magnetic resonance imaging (CMR) is the preferred instrumental examination for the diagnosis of myocarditis [36]. In a recently published study, Zhang and co-workers evaluated CMR with the use of advanced tissue characterization techniques such as late gadolinium enhancement (LGE) and highlighted that the presence of LGE was modestly associated with histopathological findings and not associated with MACE. These data suggest caution in using a single method such as LGE/standard T2 imaging for the diagnosis of ICI-associated myocarditis, especially in patients with preserved EF [37]. Furthermore, for diagnosis of myocarditis, reviewed Lake Louise Criteria suggest a combination of T2-weighted images or T2 mapping and at least one additional T1-based tissue characterization technique [38].

The gold standard for diagnosis of myocarditis is histopathological evidence on endomyocardial biopsy or autopsy [39]. Recently, Champion and Stone described two forms of ICI myocarditis, a high-grade form, in which patients with an increased inflammatory cell infiltration (>50 CD3⁺ cells/HPF) had a higher risk of fulminant clinical course, and a low-grade form (<50 CD3⁺ cells/HPF) associated with a better clinical course [40].

Treatment for patients with ICI-associated myocarditis consists in cessation of ICI therapy and immunosuppression with high-dose corticosteroids (1–2 mg/kg/day), until recovery of cardiac function and identification of the triggers. However, discontinuation of immunotherapy should be evaluated individually in case of possible myocarditis. Treatment should be started promptly, given the risk of rapid progression to fulminant disease with cardiac impairment. [41] Recent data suggested that rapid initiation of high doses of corticosteroids is associated with recovery of left ventricular function and can reduce the number of MACE, with patients treated with low doses of corticosteroids being at higher risk of severe outcome [7, 22••, 42•]. In case of therapeutic failure with

corticosteroids, the use of mycophenolate mofetil, methotrexate, calcineurin inhibitors, intravenous immunoglobulin (IVIG), antithymocyte globulin, rituximab, or infliximab is indicated. [6, 43] However, it should be noted that infliximab may be associated with worsening heart failure and is therefore not indicated in patients with moderate-to-severe heart failure.

A case of severe ICI-related myocarditis unresponsive to high-dose corticosteroid therapy treated with abatacept (CTLA-4 agonist) has been reported [44]. In addition, alemtuzumab, a humanized anti-CD52 monoclonal antibody, has shown significant resolution of cardiotoxicity in a steroid-refractory autoimmune myocarditis induced by PD-1 therapy [45]. Recently, tocilizumab, an IL-6 receptor antagonist, also showed successful improvement of symptoms in a severe ICI-related myocarditis [46].

Pericardial Disease

The use of ICIs can also bring to pericardial diseases [25••]. Clinical presentation may include pericarditis, [47, 48] pericardial effusion [47, 49, 50], or cardiac tamponade [48, 49, 51]. Pericarditis may manifest as chest pain, a new pericardial effusion on the echocardiogram, PR depression and widespread ST elevation on the ECG, or ongoing pericardial inflammation on cMRI or cardiac PET/CT [52].

Treatment for this condition is ICI withdrawal and administration of immunosuppressive therapy with corticosteroids. Colchicine and non-steroidal anti-inflammatory drugs (NSAIDs) are also used for cardiac support as in non-ICI-associated pericarditis [52]. Pericarditis and pericardial effusion can lead to cardiac tamponade, which is a complication that can be fatal. In this case, emergency pericardiocentesis and hemodynamic support appear useful [52].

Salem and colleagues observed that patients receiving anti-PD1 or anti-PDL1 therapy for lung cancer had a higher risk of pericardial diseases [25••]. The correlation between this manifestation and lung cancer is unclear. Radiotherapy and immunotherapies might synergize in patients with lung cancer. Pericardial diseases occur more frequently in patients receiving anti-PD-1 or anti-PDL-1 antibodies than those treated with anti-CTLA4. Instead, there was no difference between patients treated with monotherapy and those treated with combination therapy [25••]. The authors hypothesize that cancer patients receiving ICI after thoracic radiotherapy might be more prone to developing pericardial diseases due to the exposure of potentially shared antigens to T-cell recognition. However, the over-reported pericardial diseases might also be explained by the fact that serous illnesses are common cancer complications [53].

As for myocarditis, age does not seem to be a risk factor for ICI-associated pericardial diseases [25]. On the other hand, gender seems to play a role in the risk for these manifestations since

they appear to be more common in males than females, as demonstrated by previous studies. Nevertheless, this may simply reflect the demographics of ICI use and clinical trial enrolment [54]. Indeed, a higher number of male patients has been enrolled in clinical trials, with women being excluded for higher incidence of autoimmune diseases and lower risk of cardiovascular diseases. In fact, the true incidence of cardiac toxicity in women is underestimated and the effect of gender on irAEs has not been clearly defined. The apparent sex differences on cardiac toxicity during ICI remains controversial, and therefore further specific studies on this association are needed.

Vasculitis

Vasculitis is another important MACE. It may affect blood vessels of various sizes, and is typically classified into large, medium, and small-vessel vasculitis based on the size of the vessels involved [55]. In their pharmacovigilance study, Salem and co-workers observed vasculitis disorders associated with ICIs, particularly temporal arteritis and polymyalgia rheumatica [25••]. This inflammatory condition results in end-organ damage. Temporal arteritis is an autoimmune and inflammatory pathology of the aorta and its branches. It presents with headache, jaw claudication, amaurosis fugax or diplopia, and systemic symptoms such as fatigue, fever, and weight loss. Obviously, this condition is associated with an increase in inflammatory indices such as erythrocyte sedimentation rate and C-reactive protein [56]. The gold standard for diagnosis is temporal artery biopsy, which would demonstrate CD4⁺ T cells and macrophages organized in granulomas. Color-Doppler ultrasonography of the temporal artery is a non-invasive alternative but is not decisive. Median time to onset of toxicity is 55 days, which corresponds more or less to three ICI administration. As in myocarditis, ICI-mediated toxicity is more frequent in males than in females, and there is no age predisposition [25••]. In addition to stopping treatment, given the risk of vision loss, immunosuppressive treatment should be started early.

Large vessel vasculitis including GCA and aortitis as well as primary angiitis of the nervous system are the most common types of vasculitis associated with immune checkpoint blockade, in particular, anti-PD-1 (e.g., nivolumab) [56]. This is corroborated by the fact that single-nucleotide polymorphisms in the genes encoding PD-1 have been associated with T-cell hyperactivity at a vascular level [57]. Furthermore, Sakthivel and co-workers have shown that polymorphisms of the CTLA-4 gene, which is in close proximity to the PD-1 gene on chromosome 2, is associated with granulomatosis with polyangiitis (Wegener's; GPA) [58]. This detection was confirmed in two other studies that showed an association between CTLA-4 gene polymorphisms and GPA [59, 57].

Although the complete pathogenesis of vasculitis has not yet been elucidated, genome-wide association studies have

underlined the relationship between vasculitis and several genetic polymorphisms.

Importantly, temporal arteritis is more frequent in patients who received anti-CTLA-4 monotherapy than in those who received anti-PD1 or anti-PD-L1 monotherapy. This difference is not detectable in case of vasculitis or polymyalgia rheumatica ICI-related. However, there is no difference between patients treated with combination therapy versus monotherapy. Therefore, vasculitis can be associated with ICI therapy but at the same time they can be a paraneoplastic manifestation of many cancers, first of all melanoma [60, 61]. In particular, temporal arteritis was over-reported for patients with melanoma treated with ipilimumab. Likely, the use of ICIs could reproduce an immune micro-environment favorable for the development of vasculitis, with possible complications such as temporal arteritis and blindness [25].

Covid-19 and the Risk of Cardiotoxicity

The coronavirus disease 2019 (Covid-19) can particularly affect people with cardiovascular disease through a hyperinflammatory state with resulting cardiotoxicity. Indeed, early data suggest hyper-inflammation and depletion of T cells with increased expression of PD-1 and PD-L1 during SARS-CoV-2 infection. For this reason, blockade of these crucial pathways with ICIs might be dangerous. Moreover, promoting the immune system with a CTLA-4 agonist may be useful [62]. However, stopping ICI therapy during SARS-CoV-2 infection should be guided in a multidisciplinary approach, and the long-term effects of Covid-19-induced hyper-inflammation to the cardiovascular system need further investigations.

Conclusions

ICIs are associated with cardiovascular toxicities such as myocarditis, pericardial disease, and vasculitis. To date, only a few risk factors have been correlated with the development of ICI-mediated cardiotoxicity [6••] (Table 2). Hence, a multidisciplinary approach involving cardiologists, oncologists, and immunologists is needed for management of cardiovascular toxicities. Finally, since patients have different risks of developing ICI cardiotoxicity, a personalized clinical approach should be crucial.

The risk factor with the foremost evidence is the combination of two ICIs or concomitant treatment with other cardiotoxic drugs. An in-depth baseline assessment should be performed for all patients, and surveillance strategies on high-at risk patients should be considered for rapidly detecting irAEs, focusing on the first 12 weeks (four cycles), when the risk of developing cardiotoxicity seems to be higher. It has not been clarified whether history of previous myocardial damage

Table 2 Potential risk factors for immune checkpoint inhibitor cardiotoxicity [6, 56–58, 35, 42]

Pharmacological history
•Previous treatment with other cardiotoxic therapies (i.e., anthracyclines, anti-ErbB2 drugs, proteasome inhibitors, Raf and MEK inhibitors, VEGF tyrosine kinase inhibitors, CAR T-cell therapy)
Treatment-related factors
•Combination of two immune checkpoint inhibitors
•Concomitant treatment with other cardiotoxic therapies
•Radiotherapy-induced heart disease
Autoimmune diseases
•Rheumatoid arthritis
•Systemic lupus erythematosus
•Sarcoidosis
•Dressler's syndrome
Cardiovascular factors
•Hypertension
•Coronary artery disease
•Heart failure
•Myocardial infarction
•Myocarditis
•Diabetes mellitus
•Dyslipidemia
•↑ cTn; ↓ GLS; ECG conduction abnormalities
Tumor-related factors
•Cardiac antigens expressed in tumor
•Activation of T-cell clones against cardiac antigens
Genetic factors
•Gene polymorphisms of CTLA-4, PD-1, or PDL-1

(e.g., myocardial infarction or myocarditis) with exposure of cardiac antigens to the immune system is a risk factor for ICI-mediated cardiotoxicity. Patients with a known history of autoimmune disorders—including rheumatoid arthritis, systemic lupus erythematosus, and sarcoidosis—might be at a higher risk of autoimmune disease, especially with a previous cardiac involvement. Moreover, patients with ICI-related skeletal myositis should perform a cardiological evaluation (ECG, serum natriuretic peptides, cTn measurements, echocardiography) to exclude cardiac involvement. This cardiac assessment may also help to identify ICI-mediated myocarditis in patients presenting with ICI-related skeletal myositis.

The study of genetic factors such as gene polymorphisms of immune checkpoints, and of tumor-related factors as the expression of cardiac antigens in tumor samples, or the activation of T-cell clones against exposed cardiac antigens are intriguing, but they cannot be considered routinely available in real life (Table 2).

These immune-mediated adverse effects require even discontinuation of immunotherapy and personalized immunosuppressive treatment for the risk of fatal adverse events [63]. Since many patients are already on ICI therapy, and considering that the use of ICIs is expected to increase in the coming years, [64] more studies are needed to better understand ICI toxicities and their related risk factors and therefore also to evaluate new therapeutic perspectives.

Compliance with Ethical Standards

Conflict of Interest Flora Pirozzi, Remo Poto, Luisa Aran, Alessandra Cuomo, Giuseppe Spadaro, Pasquale Abete, Domenico Bonaduce, and Gilda Varricchi declare no conflict of interest. Maria Rosaria Galdiero is supported, in part, by a grant from the Italian Ministry of Education, University and Research (MIUR). Gianni Marone has received research funding through grants from the Regione Campania CISI-Lab, CRÈME Project, TIMING Project, and Federico II University. Carlo G. Tocchetti has received compensation from Alere for service as a consultant; is listed as an inventor on and receives royalties for Canadian Patent No. 2,613,477 (Thiol-Sensitive Positive Inotropes), issued 3 December 2013, owned by Johns Hopkins University (JHU Reference: C04755-P04755-05); and is listed as an inventor on U.S. Patent No. US20180271931 (P75NTR Antagonists and Treatment of Acute and Chronic Cardiac Disease), issued in 2018. Valentina Mercurio has received research funding from MSD.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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