Review article

Cardiotoxicity in cancer immunotherapy: from pathogenesis to prevention – narrative review

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ABSTRACT

Cancer immunotherapies, such as immune checkpoint inhibitors and chimeric antigen receptor T-cell therapy, improve survival but carry a risk of severe cardiotoxicity. Myocarditis is the most dangerous complication with high mortality, and its mechanism involves T-cell auto-aggression or cytokine storms. Risk management requires vigilance, monitoring of cardiac biomarkers, and imaging studies. Prompt treatment with high-dose glucocorticosteroids is crucial. Collaboration within cardio-oncology teams is fundamental for safety, and further research must focus on precise risk stratification to protect patients while maintaining therapeutic efficacy.

Key words: immune checkpoint inhibitors, immunotherapy, cardiotoxicity, myocarditis, cardio-oncology, immune-related adverse events, management strategies

INTRODUCTION

Immunotherapy, particularly immune checkpoint inhibitors (ICIs), has reshaped modern oncology, offering new treatment options for various malignancies [1, 2]. ICIs restore antitumor immune responses by blocking inhibitory pathways on T lymphocytes through interactions with PD-1 or CTLA-4 receptors [3, 4]. This reactivation of immune function brings new hope to patients lacking alternative therapies. However, such potent immune activation also introduces risks. A wide range of immune-related adverse events (irAEs), potentially affecting almost any organ system, can arise as a consequence [2].

Similarly, CAR-T cell therapy – a newer immunotherapeutic approach – has raised concerns over cardiotoxicity, largely due to excessive immune activation and cytokine release syndrome (CRS) [5]. ICI-related complications stem from the breakdown of immune tolerance [1, 6, 7], with clinical presentations including pericarditis, arrhythmias, heart failure, and acute coronary syndrome-like symptoms [8, 9]. Among these, ICI-associated myocarditis is one of the most severe complications [10, 11], with an estimated incidence of 0.5–1.5% [12, 13]. Symptoms can appear rapidly and are associated with high mortality rates, reaching 25–50% in severe cases [14–16]. Its subtle onset and rapid progression represent major clinical challenges [10, 16]. T-cells activated by ICIs may cross-react with myocardial antigens, causing inflammation and cardiomyocyte injury [11, 15, 17]. Patients with diabetes or autoimmune diseases are particularly vulnerable, especially during combination therapy (anti-PD-1/PD-L1 with anti-CTLA-4) [12, 18]. Despite growing awareness, tools for personalized risk stratification remain unavailable.

Diagnosing ICI-associated myocarditis is difficult due to nonspecific symptoms like fatigue, chest pain, and dyspnea, which mimic other cardiovascular conditions [10, 19]. Cardiac biomarkers, especially troponin levels, play a key diagnostic role. Elevated troponins are a strong indicator of myocarditis, while normal values support its exclusion [20, 21]. Although endomyocardial biopsy is the gold standard, ECG and echocardiography are also essential [10, 12]. Treatment involves immediate cessation of immunotherapy and initiation of high-dose glucocorticoids (GCS). In more severe cases, additional immunosuppressants may be necessary [2, 12, 22].

Given the increasing use of immunotherapy and its potentially life-threatening cardiac complications, a comprehensive understanding of this topic is essential. This review aims to summarize current knowledge on cardiovascular toxicities related to immunotherapy, including epidemiology, pathophysiology, clinical features, diagnostic approaches, and treatment strategies [8, 22].

METHODOLOGY

This narrative review was based on a systematic literature search conducted in the Scopus and PubMed databases. Keywords related to cancer immunotherapy and cardiotoxicity were used, including: "immune checkpoint inhibitors," "CAR-T therapy," "cardiotoxicity," "myocarditis," "cardiovascular adverse events," and their Polish equivalents. Publications prior to 2015 were excluded, except for those of historical or substantive relevance (e.g., key articles from 2001, 2012, and 2014 concerning the PD-1 receptor). Case reports and studies lacking specific data on cardiovascular complications or treatment outcomes were also excluded. The analysis focused on clinical trials (randomized controlled and cohort studies), systematic reviews, and meta-analyses, which provided insight into the epidemiology, mechanisms of action, and toxicity profiles of immuno-oncology therapies. Study selection was based on methodological quality, relevance, sample size (preferably >100 patients), and clinical applicability of the findings. Qualitative assessment included statistical data such as odds ratios, relative risks, and p-values to better understand risks and evaluate preventive and therapeutic strategies. The review primarily covered:

- incidence and risk factors for cardiac complications (e.g., myocarditis, arrhythmias, heart failure)
- diagnostic methods, including cardiac biomarkers, ECG, and echocardiography
- treatment and prevention strategies.

This approach enabled a comprehensive synthesis of current knowledge on ICI-related cardiotoxicity and helped identify gaps for future research.

IMMUNOLOGICAL BASIS OF ACTION OF CHECKPOINT INHIBITORS

The human immune system has self-regulatory mechanisms that ensure a balance between the effective elimination of external threats and tolerance to self-tissues. Key components include immune checkpoints, such as cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed death-1 (PD-1) receptor and its programmed death-ligand 1 (PD-L1) [3, 4]. CTLA-4 limits the excessive proliferation of T lymphocytes in the lymph nodes, primarily at the initial stage of T-cell activation [3]. In contrast, the PD-1/PD-L1 axis suppresses the activity of already activated effector cells, acting in peripheral tissues [4, 6]. During immune selection, tumor cells often acquire the ability to express checkpoint ligands, such as PD-L1, which allows them to evade recognition and elimination by T lymphocytes, thereby weakening the antitumor response in the tumor microenvironment [4]. The reactivation

of T lymphocytes and the restoration of their cytotoxic capabilities against tumor cells are possible by blocking the interaction of these receptors with their ligands through the use of ICIs. ICIs include monoclonal antibodies directed against CTLA-4 (such as ipilimumab) [1, 23], as well as against PD-1 (such as pembrolizumab, nivolumab) and PD-L1 (such as durvalumab, avelumab, atezolizumab) [6, 24]. ICI therapy has brought significant clinical benefits, improving the survival of patients with advanced cancers such as melanoma, non-small cell lung cancer, renal cancer, urothelial cancer, head and neck cancer, and lymphomas [3, 7, 23, 24].

The mechanisms of action of CTLA-4 and PD-1/PD-L1 inhibitors are different. Ipilimumab, a representative of CTLA-4 inhibitors, blocks CTLA-4 and affects the initial phases of T-cell activation in the lymph nodes, increasing the number of effector T-cells and regulatory T-cells, which are responsible for auto-immunization [1, 3, 23]. In contrast, PD-1 and PD-L1 inhibitors, such as nivolumab, pembrolizumab, and atezolizumab, act in peripheral tissues, blocking signals that inhibit lymphocyte activity, which allows for the reactivation of T lymphocytes in the tumor microenvironment [6, 24]. Both groups can have similar cardiac complications, such as myocarditis, pericarditis, or cardiac arrhythmias [6, 7, 9]. However, combination therapy (CTLA-4 + PD-1/PD-L1) is associated with a higher probability of severe adverse events, as confirmed by clinical trials [14, 16]. A summary of the main groups of immuno-oncology drugs, their mechanisms of action, and the most common cardiac complications is presented in table 1.

Beyond ICIs and CAR-T therapy, other forms of immunotherapy are being developed, such as inhibitors of the LAG-3 (lymphocyte-activation gene 3) and TIGIT (T-cell immunoreceptor with Ig and ITIM domains) checkpoints. Although the therapeutic potential of these drugs is high, their safety and toxicity profiles still require extensive clinical investigation [2, 22]. An example of a new inhibitor is relatlimab, which blocks LAG-3 [22]. The dynamic development of combination therapies and the introduction of new immunomodulatory mechanisms are paving the way for more effective and safer cancer treatment strategies [2].

It should be remembered that the use of ICIs is associated with a breach of physiological immune tolerance mechanisms, and the risk of an uncontrolled immune response against self-tissues increases because the "brakes" controlling T-cell activity are deactivated. As a result, irAEs may occur [2, 7]. These include cutaneous, gastrointestinal, and endocrine symptoms, as well as cardiac complications [2, 7].

MECHANISMS LEADING TO MYOCARDIAL DAMAGE

Immune-induced myocarditis (ICI-myocarditis) is one of the most severe but rare irAEs [14]. The incidence of myocarditis among patients treated with immune checkpoint inhibitors (ICIs) is approximately 1.14%, and the mortality rate in diagnosed cases reaches up to 50% [14]. A statistically significant difference ($p < 0.01$) in the incidence of myocarditis has also been demonstrated between combination therapy (anti-CTLA-4 + anti-PD-1) and monotherapy [16]. The underlying cause of ICI-myocarditis is uncontrolled activation of the immune system, particularly T lymphocytes, which trigger an autoimmune reaction against cardiomyocytes [11, 15, 17]. The inflammation results from infiltration of the myocardium by activated CD4+ and CD8+ T-cells. Cardiomyocyte necrosis and diffuse lymphocytic infiltrates have been identified in both biopsy and autopsy histopathological examinations [6, 11, 15]. These lymphocytes attack antigens structurally similar to tumor antigens, a phenomenon known as molecular mimicry [17]. Studies have also demonstrated significantly elevated levels of pro-inflammatory cytokines – interleukin 6 (IL-6), interferon gamma (IFN-γ), and tumor necrosis factor alpha (TNF-α) – which intensify cardiomyocyte injury by inducing an inflammatory response [17, 22]. In some cases, lymphocytes infiltrating the myocardium express cytotoxic markers such as perforin or granzymes [11, 22].

Table 1. Characteristics of selected groups of immuno-oncology drugs and their cardiotoxicity.

Drug class	Mechanism of action	Most common cardiac complications	Examples of drugs
CTLA-4 inhibitors	Blockade of CTLA-4 leads to increased T-cell activation at an early stage of the immune response, enhancing the cytotoxic effect but also the risk of auto-immunization.	• myocarditis • pericarditis • arrhythmias • less commonly takotsubo cardiomyopathy	• ipilimumab
PD-1/PD-L1 inhibitors	Inhibition of the PD-1/PD-L1 interaction unblocks T-cells in peripheral tissues, allowing for the reactivation of the antitumor response.	• myocarditis • arrhythmias • pericarditis • takotsubo cardiomyopathy	• nivolumab • pembrolizumab • atezolizumab • durvalumab • avelumab
CAR-T cell therapy	Genetic modification of a patient's T-cells to recognize and attack specific tumor antigens (e.g., CD19).	• cytokine release syndrome: hypotension, heart failure, arrhythmias, pulmonary edema	• tisagenlecleucel • axicabtagene ciloleucel
LAG-3 and TIGIT Inhibitors	Blockade of new checkpoints (LAG-3, TIGIT) enhances T-cell activity, often in combination with other PD-1/PD-L1 inhibitors.	data are limited; potential risk of autoimmune complications and cardiotoxicity requires further investigation	• relatlimab (LAG-3) • tiragolumab (TIGIT)

Current research indicates that the complex basis of ICI-induced cardiotoxicity involves cellular (autoreactive lymphocytes), humoral (cytokines), and structural (myocardial damage) components [11, 17, 22].

It is important to note that rapidly progressing myocarditis may occur even after the first doses of ICIs. Clinical presentations vary, ranging from asymptomatic troponin elevation to arrhythmias, fulminant heart failure, or sudden cardiac death [9, 12, 15]. Risk factors include a history of cardiovascular disease, autoimmune disorders, previous immunomodulatory therapy, and the use of combination checkpoint blockade (anti-CTLA-4 + anti-PD-1) [6, 18]. There have been reports of initially asymptomatic myocarditis cases with fatal outcomes, including two patients who died from ventricular arrhythmia only days after treatment initiation [15, 16]. Unfortunately, predictive markers for identifying patients at risk of developing myocarditis or early, potentially reversible symptoms remain lacking.

CAR-T therapy (chimeric antigen receptor T-cell therapy) is a modern oncological treatment method involving genetic modification of a patient's T-cells to recognize and destroy tumor cells through specific antigens [5, 23, 25]. Agents such as tisagenlecleucel and axicabtagene ciloleucel are primarily used in selected leukemias and lymphomas [5]. CRS, the most significant cardio-oncological complication of CAR-T therapy, affects up to 60% of patients, with cardiotoxic symptoms such as hypotension, arrhythmias, and heart failure observed in about 25% of cases [5, 8, 26]. CRS results from a sudden release of pro-inflammatory cytokines, particularly IL-6, leading to systemic inflammation and multiorgan damage, including myocardial injury [8, 26].

Modern cancer immunotherapy methods such as ICIs and CAR-T therapy differ in their mechanisms of cardiotoxicity. CRS is the primary mechanism of toxicity in CAR-T therapy. It causes a rapid release of cytokines including IL-6, resulting in inflammation, hemodynamic instability, and multi-organ damage, including the heart [5, 8, 26]. A significant correlation has been demonstrated between CRS severity and the incidence of arrhythmias ($p = 0.03$) [8]. Pulmonary edema, arrhythmias, and shock are frequently observed during CRS and require intensive care [5, 8]. Tocilizumab – an antibody blocking the IL-6 receptor – is an effective treatment for mitigating CRS symptoms and reducing cardiac complications [5].

In conclusion, unlike ICI-induced myocarditis, which is primarily mediated by autoimmune reactions against self-tissues, cardiotoxicity in CAR-T therapy is largely cytokine-driven and inflammatory in nature [5]. Additionally, immune effector cell-associated neurotoxicity syndrome (ICANS), which may coexist with arrhythmias and circulatory failure, further complicates the clinical picture of CAR-T-related cardiotoxicity.

OTHER FORMS OF ICI-INDUCED CARDIOTOXICITY

Although myocarditis is the most recognized and severe manifestation of ICI-induced cardiotoxicity, growing evidence indicates an increased risk of other, sometimes mild but potentially dangerous cardiovascular complications. These may present in a delayed or atypical manner during combination therapy or monotherapy [6–8]. The most common conduction and rhythm disorders are atrial fibrillation, while supraventricular and ventricular tachycardias, as well as second- and third-degree atrioventricular blocks, are less frequently observed [9, 19]. Their onset may result from damage to the conduction system, inflammatory infiltrates, or secondary fibrosis [6, 19]. In some cases, electroanatomical changes resembling Brugada syndrome or long QT syndrome have also been observed [6].

Endothelial dysfunction is another potential form of cardiotoxicity, which may lead to vasculitis, elevated blood pressure, and accelerated atherosclerosis [4, 7, 8]. Even in patients without significant coronary artery disease, exacerbation of pre-existing hypertension and coronary events have been reported during ICI therapy, including ST-elevation myocardial infarction [13].

Pericardial effusion is also possible and can lead to cardiac tamponade [1, 6]. However, in most cases, the course is oligosymptomatic and limited to a small accumulation of fluid in the pericardial sac. Laboratory analysis of the fluid typically shows a predominance of lymphocytes and elevated concentrations of inflammatory cytokines, while imaging reveals signs of pericardial irritation [6].

Takotsubo syndrome, also known as stress cardiomyopathy, has also been linked to ICI therapy; however, due to its nonspecific symptoms and diagnostic difficulties, its actual incidence is likely underestimated [6]. The underlying mechanism is believed to involve strong activation of the sympathetic nervous system and secondary myocardial injury, potentially with an inflammatory component [6]. The clinical presentation may mimic myocardial infarction with negative coronary angiography findings, and left ventricular function usually recovers within 2 to 3 days [6].

The increasing number of patients undergoing immunotherapy and the expanding use of ICIs in treating various cancer stages necessitate careful patient monitoring. It is recommended to regularly perform at least ECG, cardiac biomarkers (troponins, NT-proBNP), and imaging studies in patients receiving combination therapy or those with multiple risk factors [7, 8, 13].

DIAGNOSIS OF CARDIOTOXICITY ASSOCIATED WITH CANCER IMMUNOTHERAPY

In the case of immune checkpoint inhibitors (ICIs) and CAR-T therapy, the diagnosis of cardiovascular complications requires

a multidimensional approach, incorporating imaging techniques, clinical evaluation, and biomarkers.

Cardiac troponins, particularly high-sensitivity variants (hs-cTnI, hs-cTnT), are key biomarkers in diagnosing myocarditis induced by cancer immunotherapy. Elevated troponin levels are observed in the vast majority of patients with clinically manifest myocarditis – according to registry data, in up to 94% of cases [12, 15]. In a retrospective study of 101 patients treated with ICIs, elevated hs-cTnI levels were associated with a 5.6-fold increased risk of major adverse cardiovascular events (HR = 5.6; 95% CI: 2.1–14.8; p <0.001) [6]. Moreover, patients with troponin concentrations above 1 ng/mL had significantly higher in-hospital mortality (27%) compared to those with levels below 1 ng/mL (8%) (p = 0.009) [12]. A prospective study on biomarker surveillance during immunotherapy revealed that 34% of patients showed elevated hs-cTnI within the first 6 weeks of treatment, and 9% had subclinical myocarditis confirmed by cardiac MRI [21]. Troponin elevation occurred 2–7 days prior to the onset of clinical symptoms, making it a valuable early detection tool for cardiotoxicity [1, 10]. Furthermore, each 0.01 ng/mL increase in hs-cTnI was associated with a 1.4-fold increase in the likelihood of major adverse cardiovascular events (HR = 1.4; 95% CI: 1.1–1.9; p = 0.02) [6]. Data regarding CAR-T therapy are more limited. In an analysis of 137 patients, 38% had elevated troponin levels, mainly in the context of cytokine release syndrome (CRS), with significantly higher risk of ventricular arrhythmias in this subgroup (OR = 3.2; 95% CI: 1.1–9.5; p = 0.03) [5]. Despite their high sensitivity, troponins are not specific for myocarditis, and interpretation must take into account the clinical context and imaging findings. Their utility extends beyond diagnosis, as elevated troponin levels are also associated with a worse prognosis, higher major adverse cardiovascular events (MACE) risk, and increased mortality.

Natriuretic peptides, including B-type natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP), are helpful in evaluating volume overload and left ventricular dysfunction. Although not specific for myocarditis, they can support the diagnostic process when interpreted alongside symptoms and other test results [6, 11, 12]. Retrospective studies show that 50–70% of patients with ICI-associated myocarditis had elevated NT-proBNP levels, especially those with systolic dysfunction [6, 14]. NT-proBNP levels exceeding 1000 pg/mL were associated with an increased risk of heart failure-related hospitalization (OR = 3.9; 95% CI: 1.6–9.5; p = 0.002) and higher 30-day mortality (19% vs. 6%; p = 0.03) [6, 12]. A prospective study demonstrated that concurrent elevation of hs-cTnI and NT-proBNP improved diagnostic specificity for myocarditis (AUC = 0.87; 95% CI: 0.78–0.96) and was a strong predictor of MACE [1, 21]. Elevated NT-proBNP in combination with echocardiographic signs of systolic dysfunction was associated with an increased risk of arrhythmias and prolonged hospitalization [11, 19]. Though limited, data on CAR-T therapy suggest that BNP and NT-proBNP elevations are often secondary to severe CRS. In a study of 137 patients, NT-proBNP levels above 900 pg/mL were linked to greater likelihood of ICU admission and inotrope use (OR = 2.6; 95% CI: 1.1–6.1; p = 0.04) [5].

There is increasing evidence for the diagnostic and prognostic relevance of natriuretic peptides and cardiac troponins in immunotherapy-related myocarditis. However, clinical application must be cautious. Elevation of these markers is not specific for myocarditis and may also result from sepsis, heart failure, or CRS. Additionally, the absence of clearly defined thresholds and limited prospective validation necessitate comprehensive interpretation based on symptoms, imaging, and potentially endomyocardial biopsy. Further research with larger cohorts and stratified analyses is required to fully establish their role in risk assessment and therapeutic decision-making.

Although inflammatory markers such as CRP and ESR are neither sensitive nor specific, they may be useful in assessing inflammatory activity. CRP levels >10 mg/L were observed in 71% of patients with cardiovascular toxicity during ICI therapy [9]. Autoimmune tests (ANA, RF, pANCA) may assist in differential diagnosis, although only 20–25% of myocarditis patients had a positive result for any of these [17]. Renal function markers and liver enzymes may be altered in patients with systemic immunotherapy toxicity, but they are not useful in diagnosing myocarditis. In contrast, peripheral blood count may show eosinophilia or lymphocytosis, indicative of eosinophilic or lymphocytic myocarditis subtypes [16].

Electrocardiographic abnormalities are present in 89–94% of patients with ICI-induced myocarditis. ECG may reveal arrhythmias (including ventricular), atrioventricular conduction blocks, or ischemic changes. The most common findings include nonspecific repolarization disturbances, right bundle branch block, and sinus tachycardia [20, 21].

Echocardiography is a fundamental modality for assessing left ventricular function, wall motion abnormalities, and pericardial effusion. However, LVEF may remain normal in early ICI-myocarditis; studies show that up to 50% of patients have preserved LVEF [1, 6, 11]. In such cases, further imaging is warranted.

Cardiac magnetic resonance (CMR) is the gold standard for non-invasive myocarditis diagnosis. It enables assessment of systolic function, tissue necrosis/fibrosis (via gadolinium enhancement), and myocardial edema (T2-weighted imaging). The Lake Louise Criteria offer high specificity (up to 90%) and sensitivity (up to 87%) for active myocarditis [17, 22]. In ICI-treated patients, CMR abnormalities were observed in up to 76% of those with confirmed myocarditis [11].

Endomyocardial biopsy (EMB) remains the histopathological reference standard for diagnosing ICI-myocarditis, as it provides direct evidence of inflammatory infiltrates, cardiomyocyte necrosis, or features of ICI-related toxicity [11, 12]. EMB is particularly indicated when clinical presentation is ambiguous or other methods yield inconclusive results, despite its invasive nature. In a large case series, CD8+ T-cell infiltration and PD-L1 expression were identified as characteristic of ICI-myocarditis [1, 22]. The diagnostic sensitivity of EMB is estimated at 60–70%, and increases substantially when biopsy is guided by regions of abnormality detected on cardiac MRI [6, 11].

RISK STRATIFICATION AND DIFFERENTIAL DIAGNOSIS

Excluding other causes of cardiac symptoms is essential when ICI-myocarditis is suspected. Ischemic heart disease should be considered first, particularly in older patients or those with a history of cardiovascular conditions, as coexistence may worsen the clinical course. Ischemia can be differentiated from myocarditis using imaging modalities such as coronary angiography or coronary CT angiography. Infectious myocarditis is also an important consideration, given the similarity in clinical presentation and laboratory results – especially elevated cardiac biomarkers and arrhythmias [12]. The differential diagnosis should additionally include toxic cardiomyopathies related to previous treatment with anthracyclines, tyrosine kinase inhibitors, or radiotherapy [4]. To distinguish immune-mediated myocarditis from other causes of myocardial injury, cardiac magnetic resonance imaging and, where applicable, endomyocardial biopsy results should be used [11, 17]. It is important to note that cancer immunotherapy may both induce new cardiovascular conditions and exacerbate pre-existing ones [2]. Consequently, interdisciplinary cooperation involving a cardiologist, oncologist, and immunologist is fundamental for effective differential diagnosis and optimal patient care [8].

High-risk patients require special surveillance due to the fulminant and unpredictable nature of ICI-myocarditis [5, 27]. This includes individuals with heart failure, cardiomyopathies, arrhythmias, and coronary artery disease who are treated with combination regimens such as CTLA-4 and PD-1/PD-L1 inhibitors or CAR-T therapy [5, 18, 27]. Prior to the initiation of immunotherapy, a comprehensive cardiovascular evaluation is recommended, including high-sensitivity cardiac troponin (hs-cTnI or hs-cTnT), NT-proBNP, electrocardiogram (ECG), and echocardiography [16, 21, 27]. Cardiac magnetic resonance imaging should be considered a reference modality in selected patients, particularly in cases of diagnostic uncertainty [11, 27]. During the first 6–8 weeks – when the risk of myocarditis is highest – regular monitoring of cardiac biomarkers is advised, typically every 1–2 weeks [21, 27, 28]. Troponin elevation occurs in approximately 34% of patients, with some developing subclinical myocarditis, as demonstrated in prospective studies [21, 29]. A rise in troponin levels may precede the onset of clinical symptoms by several days, underscoring the value of systematic measurements [1, 10, 27]. NT-proBNP is a marker of volume overload or impaired left ventricular function [16, 27]. Particular attention should be given to asymptomatic patients with elevated NT-proBNP, as this may indicate the need for additional diagnostics or discontinuation of immunotherapy [20, 27].

Regular ECG and echocardiographic monitoring – both at scheduled intervals and in response to new symptoms – enables early detection of arrhythmias, deterioration in systolic function, and signs of pericardial involvement [2, 7, 27]. Monitoring hemodynamic parameters and the early application of imaging tools to detect inflammation and myocardial damage are also recommended [27]. Patients with abnormalities should be urgently referred for cardiology consultation and, if indicated, hospitalized for further diagnostics and initiation of appropriate immunosuppressive therapy [5, 6, 27, 28].

Studies show that long-term cardiac complications, such as chronic heart failure, may develop even after resolution of the acute myocarditis episode, emphasizing the need for prolonged follow-up and cardiovascular care [29]. Early diagnosis of cardiac involvement reduces the risk of serious complications, including MACE, and enables the safe continuation of anticancer therapy [5, 21, 27, 28].

TREATMENT

To prevent the development of cardiotoxicity symptoms induced by cancer immunotherapy, early recognition and initiation of appropriate therapeutic measures are essential. Early intervention may prevent permanent myocardial damage and reduce the risk of serious complications such as heart failure or life-threatening arrhythmias [1, 6, 11]. The first step is to discontinue immuno-oncological treatment in patients presenting with moderate or severe cardiotoxicity symptoms, with the decision made by an interdisciplinary team consisting of an oncologist, cardiologist, and immunologist [2, 8]. Hospital monitoring of the patient is necessary, and all therapeutic actions must take into account the concurrent treatment of the malignancy, aiming to balance the effectiveness of cancer therapy with patient safety [1, 6, 11, 22].

Treatment of ICI-myocarditis is primarily based on immunosuppression. Early administration of high-dose GCS, typically methylprednisolone at 1–2 mg/kg/24 h, is crucial to reduce mortality and the risk of myocardial injury. Clinical studies have shown that de-

laying GCS therapy beyond 24–48 h from diagnosis significantly increases the risk of death (HR = 2.5; 95% CI: 1.3–4.8; p = 0.007) [12, 16]. Pulse therapy with methylprednisolone (1 g/24 h for 3 days) is used in patients with severe myocarditis or hemodynamic instability. This method significantly reduces the risk of cardiac arrest compared to standard GCS therapy (HR = 0.4; 95% CI: 0.2–0.9; p = 0.02) and shortens hospitalization by approximately 5 days (p = 0.01) [22]. GCS are then gradually tapered over at least 4–6 weeks to prevent relapse. Despite high-dose immunosuppression, 30–40% of patients show resistance or relapse, requiring second-line immunosuppressive agents such as mycophenolate mofetil, azathioprine, or cyclosporine. The addition of these drugs reduces the risk of progression to heart failure by 35% (HR = 0.65; 95% CI: 0.45–0.94; p = 0.03) [11]. In recent years, biological therapies for resistant forms of myocarditis have gained interest. The T-cell costimulation modulator abatacept has shown potential to reduce mortality in patients unresponsive to standard treatment by about 20% (p = 0.04) [22]. Other biological agents under investigation include infliximab (an anti-TNF-α antibody) and tocilizumab (an anti-IL-6 antibody), which may serve as future treatment options. However, it is important to note the increased likelihood of infectious complications during immunosuppressive therapy. The risk of opportunistic infections affects 15–25% of patients, and immunosuppression increases this risk nearly 3-fold (HR = 3.2; 95% CI: 1.8–5.5; p < 0.001) [2, 8]. Therefore, close clinical monitoring, prevention of fungal and viral infections, and rapid diagnosis of potential infections are also necessary.

Treatment of ICI-myocarditis should be comprehensive, in line with current cardiology guidelines, and include symptomatic management. According to current guidelines from the European Society of Cardiology (ESC) and the American College of Cardiology/American Heart Association (ACC/AHA), patients with reduced left ventricular ejection fraction or symptoms of chronic heart failure should be considered for therapy with ACE inhibitors, β-blockers, mineralocorticoid receptor antagonists, and loop diuretics [6, 11, 20]. These therapies should be used cautiously, especially during the acute phase of myocarditis, when their application may be limited by hypotension and hemodynamic instability. Observational studies show that left ventricular function improves in 40–60% of patients within 3–6 months of initiating symptomatic treatment [12, 21]. However, data from large studies indicate that even after resolution of the acute cardiotoxic episode, chronic heart failure may develop, requiring ongoing medical care [29]. Arrhythmias – both supraventricular (e.g. atrial fibrillation) and ventricular (e.g. ventricular tachycardia) – occur in 20–30% of patients with ICI-related myocarditis and often correlate with the severity of inflammation [6, 9, 12]. Treatment of arrhythmias includes antiarrhythmic drugs (e.g. amiodarone), electrical cardioversion if hemodynamic instability is present, and consideration of implantable cardioverter-defibrillators (ICD) in patients with persistent left ventricular dysfunction to reduce the risk of sudden cardiac death [6, 11, 19]. Reports suggest that in patients with sustained ejection fraction <35% 3 months after a myocarditis episode, the risk of ventricular arrhythmia can reach 20% [11, 19].

During immunotherapy, myocarditis is associated with coagulation system activation and increased risk of thromboembolic events. In patients with severe left ventricular dysfunction, atrial fibrillation, or unexplained dyspnea, anticoagulation prophylaxis should be considered using NOACs (non-vitamin K oral anticoagulants) or VKAs (vitamin K antagonists) [5, 6, 20]. Observational data show that prophylaxis reduces the risk of pulmonary embolism and stroke by 40–50% (HR = 0.52; 95% CI: 0.33–0.81; p = 0.004) [20]. Supportive care should include blood pressure control, correction of electrolyte imbalances, avoidance of cardiotoxic medications, and lifestyle modifications – especially limiting physical exertion during the acute myocarditis phase [6, 11, 21]. The entire process requires regular assessments of patient status, imaging, and laboratory evaluations, with adjustments to the treatment plan based on disease progression.

Reintroduction of ICIs after a cardiotoxicity episode, especially myocarditis, carries significant clinical risk. The recurrence rate of ICI-myocarditis after resuming immunotherapy may reach 25–50% in patients who experienced a severe initial episode [12]. According to current recommendations, reintroduction should only be considered after full resolution of clinical symptoms, normalization of cardiac biomarkers (troponin, BNP), recovery of left ventricular ejection fraction, and absence of myocardial inflammation on cardiac MRI [10, 11, 27]. Other cardiac causes of symptoms must also be ruled out [9]. To reduce the risk of recurrence, monotherapy is preferred over combination therapy. During reintroduction, close cardiac monitoring is essential, including regular hs-TnI and NT-proBNP measurements and ECG every 1–2 weeks for the first 2 months of therapy [21]. In some cases, prophylactic use of immunomodulators such as tocilizumab or low-dose GCS is considered [4, 22]. Decisions regarding reintroduction should be made by a team of specialists including an oncologist, cardiologist, and immunologist [2, 6, 20]. The 2023 guidelines from the American Society of Clinical Oncology (ASCO) state that ICI reintroduction should be conducted in multidisciplinary centres under intensive monitoring, with consideration of prophylactic immunosuppressive therapy and adjustments to treatment protocols to minimize the risk of myocarditis recurrence [28].

Treatment of ICI-myocarditis is not always successful with standard GCS-resistance to GCS may occur in approximately 30% of patients [12]. In such cases, new immunosuppressive strategies

such as IL-6 inhibitors (tocilizumab), Janus kinase inhibitors (ruxolitinib), TNF-α inhibitors, or cyclosporine are gaining importance [11, 22]. Advances in therapy are increasingly based on personalized approaches, identifying cardiotoxicity biomarkers and risk factors. Measurement of proinflammatory cytokines, serum PD-L1 levels, and HLA (human leukocyte antigens) profiling are promising diagnostic tools [3, 18, 23]. Research is also ongoing into new molecular biomarkers and predictive models based on artificial intelligence [17]. Clinical trials are focused on improving the safety of immunotherapy, including testing modified dosing regimens, cardioprotective strategies, and immuno-oncology therapies with reduced immunogenicity. In the future, more selective therapies can be expected that maintain antitumor efficacy while reducing cardiovascular risk [1, 4, 6, 22].

DISCUSSION AND CONCLUSIONS

Advancements in cancer immunotherapy, including immune checkpoint inhibitors and CAR-T cell therapies, have significantly improved the prognosis for many patient groups and transformed the landscape of oncological treatment. However, the growing number of reports on cardiotoxicity underscores the need for increased vigilance and further dedicated research in this area. Cardiovascular complications such as myocarditis, pericarditis, arrhythmias, or CRS-related cardiac dysfunctions present with diverse and often unpredictable clinical manifestations – ranging from asymptomatic elevations in cardiac biomarkers to fulminant heart failure with high mortality.

Based on current evidence, a deeper understanding of the immunological and molecular mechanisms leading to myocardial damage is essential. Equally important is the development of sensitive and specific biomarkers that enable the early identification of patients at risk. This will require close, interdisciplinary collaboration between oncology, cardiology, and immunology teams, as well as prospective, multicentre studies conducted in diverse patient populations, including those with pre-existing cardiovascular disease.

Early diagnosis and immediate therapeutic intervention – most often involving high-dose GCS-based immunosuppression – are critical for improving clinical outcomes and reducing mortality. Routine monitoring of cardiac biomarkers, imaging studies, and adherence to international guidelines such as those from the ESC and ASCO provide a framework for safe treatment delivery. Rapid response to early warning signs is essential to prevent irreversible cardiac injury.

In parallel, ongoing research is needed to better characterize mechanisms of immune-related cardiotoxicity and to develop cardioprotective strategies, including novel immunomodulatory agents. A top priority is the validation of emerging biomarkers and the creation of predictive models for precise, individualized risk stratification before the initiation of immunotherapy. Only through well-organized, multidisciplinary cardio-oncology care will it be possible to fully harness the therapeutic potential of modern immunotherapies while effectively minimizing the risk of severe, and potentially fatal, cardiac complications.

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