

An issue that should be considered is the potential toxicity of ICIs to the cardiovascular system

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Abstract. An important consideration is the potential cardiovascular toxicity of immune checkpoint inhibitors (ICIs) in cancer therapy, given their increasing popularity and revolutionizing effects on certain treatment regimens. However, ICIs also exhibit unavoidable side effects such as immune-related adverse events (irAEs), which are particularly significant due to their interaction with underlying diseases. This review aims to explore the reported cardiovascular toxicity in patients treated with ICIs, providing insights into potential mechanisms, monitoring methods, and management strategies for the rational use of these drugs. The awareness of ICIs' use is crucial for clinicians as these adverse immune events can interact with the patient's underlying disease. This review focuses on cardiovascular toxicity reported in patients after ICI usage, aiming to elaborate potential mechanisms, monitoring methods, and management strategies that may inspire rational clinical use of ICIs.

Keywords: Immune checkpoint inhibitors; cardiovascular toxicity; Immune-related adverse events.

1. Introduction

Cancer and cardiovascular have a lot in common when it comes to risk factors, making them the leading global mortality factors [1]. It was believed that the number of cancer cases will keep rising with longer lifespans in the future decades. In another survey on the positive effects of vegetables and fruits on cardiovascular disease, completed by Jun Wang et al., investigators identified 3,677 cases and 5,466 all-cause deaths among 73,668 people [2]. This undoubtedly reflects the fact that the development of modern medicine has not resolved the root causes of all the diseases that pose a significant threat to human health.

However, it is not uncommon for tumors and cardiovascular disease to co-occur in the same patient and may be further exacerbated by prolonged survival and exposure to anticancer therapy [3]. More worryingly, the use of ICIs in oncology in recent years has led to cardiovascular system involvement in cancer patients, even if these patients were assessed for this prior to the administration of the drug. Earlier conventional anticancer treatments have been shown to have established cardiotoxicity, therapies have undergone a paradigm shift in side effects due to the use of ICIs [2]. Not surprisingly, the use of ICIs can result in the involvement of almost every organ or system, such as the digestive system, the nervous system, the endocrine system, the liver or the lungs [4], and the involvement of the cardiovascular system is particularly important for the patient's prognosis, as severe damage to the myocardium or to the cardiac conduction system can have a direct impact on the life expectancy of the patient as well as on the development of cancer (Fig. 1). These adverse reactions, born as a result of therapeutic innovations, do not occur in every patient, but their lethality is undeniable [5]. Therefore, early identification and intervention of these side effects (mainly referred to as irAEs) to ensure that patients benefit from immunotherapy rather than being affected by side effects into complications that should not have occurred [4].

But, to date, the specific pathogenesis of ICI-induced adverse cardiovascular events (including molecular pathways, cellular signaling, etc.) has yet to be fully elucidated, and we are currently limited to retracing the manifestations of toxicity and symptomatic treatments for the clinical manifestations. In addition, there needs to be more statistical studies on the various subtypes of clinical manifestations of cardiovascular irAEs, such as the incidence rate, how different risk factors affect the severity of morbidity, and so on.

This review will describe the possible mechanisms by which ICIs mediate adverse cardiovascular events, the four common reported clinical presentations, and the corresponding therapeutic management strategies, which will help frontline clinicians to be as aware as possible of the possible dangers that may arise when applying ICIs, to manage the dangers when they do arise, and to manage the dangers when they have survived the acute phase. Mastering the balance between risk and benefit will be a mandatory requirement for oncologists to treat diseases with ICI in the new stage.

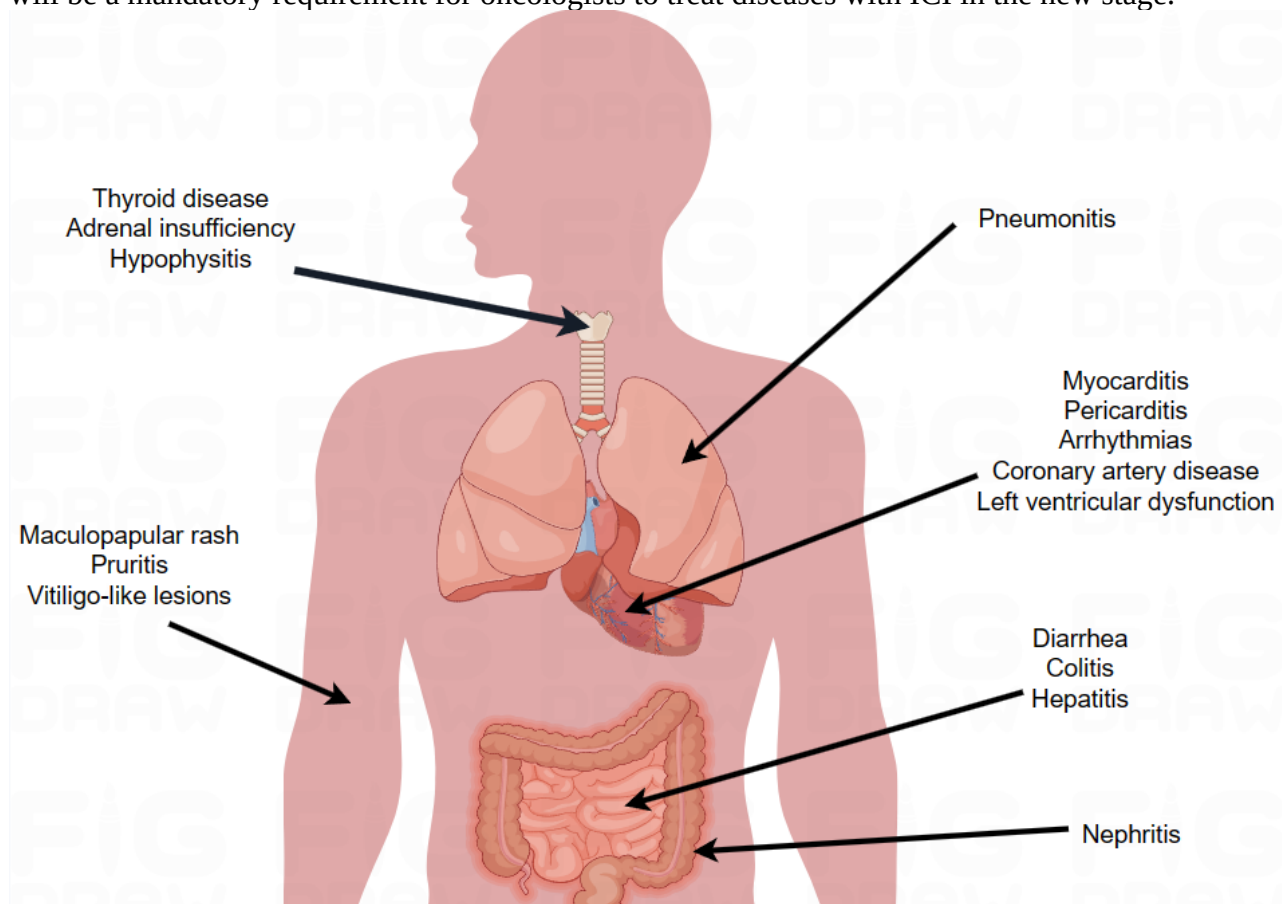


Fig. 1 The immune system can potentially impact any organ system through, with the skin and endocrine system being particularly susceptible. The gastrointestinal tract, kidneys, and lungs are commonly affected areas, while cardiovascular immune-related diseases are infrequent but can have significant implications [6].

2. Potential cardiotoxicity of immune checkpoint inhibitors

Although the cardiovascular toxicity of ICIs was rarely mentioned in early clinical trials, in recent case series, about 1%-2% of patients were affected by ICIs-induced myocarditis, and subsequently, pericardial disease, arrhythmias, and so on have been reported. Data suggest that vasculitis and thrombosis of arteries and veins are associated with the use of ICIs [1]. The above adverse reactions, which include rare but fatal diseases, remind us once again that accurately assessing the balance between benefits and risks in the application of ICIs is a challenging issue [5]. There is evidence that Cardiovascular toxicity can be caused by immune-mediated adverse events caused by ICIs, Symptoms of pericardial disease include vasculitis, arrhythmias HF myocarditis, and cardiomyopathy. In addition, circulatory-related disorders such as neutropenia, thrombocytopenia, and acquired hemophilia have been reported [7].

3. Potential mechanisms of negative cardiovascular events based on the application of ICIs.

The emergence of cancer immunotherapy, in contrast to traditional anti-cancer therapy, is based on the modern medicine's ability to enhance immune evasion against cancer cells. This approach involves up-regulating the body's natural defense mechanisms to effectively combat cancer cells. The emergence of immunotherapy has brought about a paradigm shift and unprecedented advancements in the realm of cancer treatment. The focus of this review is on ICIs; however, it should be noted that immunotherapy encompasses monoclonal antibodies, targeted therapy for immune cells, and other significant subtypes as well. The ICIs are a kind of monoclonal antibodies that inhibit the negative regulators of T-cell immune responses. CTLA-4, PD-1 as well as PD-L1 antibodies are the most popular ones among all the ICIs.

The distribution of PD-1 is not uncommon, as it is present on the surface of T cells, B cells, monocytes, as well as other cellular entities. Upon binding to its ligand (PD-L1), PD-1 exerts a negative regulatory impact on the proliferation and migration of T cells. The reason behind the reactivation of the immune system and subsequent tumor eradication lies in the administration of PD-1 or PD-L1 treatments. The CTL-4 molecule functions as a co-inhibitory factor that impacts both T cells and conventional T cells. By competing with CD28 for B7 binding, CTL-4 effectively hinders the positive regulatory activity of T cells [8]. As previously mentioned, ICIs have the potential to cause multi-organ involvement, including myocarditis and heart failure. Data suggests that patients receiving injectable ICIs are 11 times more likely to develop myocarditis compared to those not receiving them, with mortality rates as high as 50% [9]. The mechanisms and pathways associated with the mechanism of poorly understood; however, clinical manifestations can provide insights into toxicology (Fig. 2).

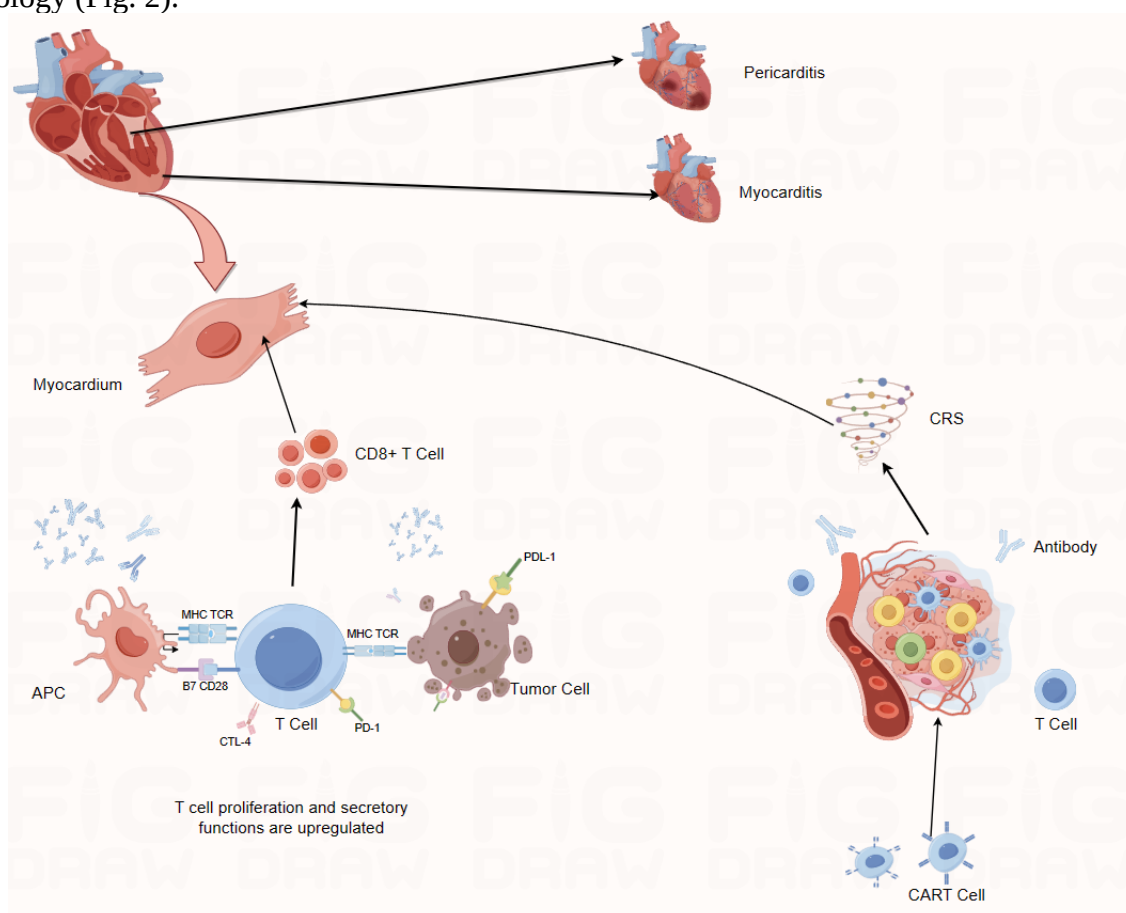


Fig. 2 Mechanisms underlying immunotherapy-induced cardiotoxicity: Suppression of CELA-4 expression results in of CD8⁺ T cells within cardiac tissue. Chimeric antigen receptor T-cell therapy elicits an inflammatory response leading to cytokine release syndrome (CRS).

4. Management strategies for cardiotoxicity of immune checkpoint inhibitors

Given that traditional cardiovascular risk factors and a history of prior cardiovascular disease are not uncommon in patients preparing for anticancer therapy, it is clearly irresponsible to skip the relevant assessments and use immunotherapy directly. In terms of categorizing the outcomes of pre-treatment assessments, although there is a lack of consistent criteria, it is feasible, after expert discussion, to broadly categorize cardiovascular-related irAEs into four types of outcomes according to the probability that they may occur: low-risk (less than 2%), intermediate-risk (2% to 9%), high-risk (10% to 19%), and very high-risk (greater than 20%) [1].The specific classification rules are shown in the table below (Fig 3).

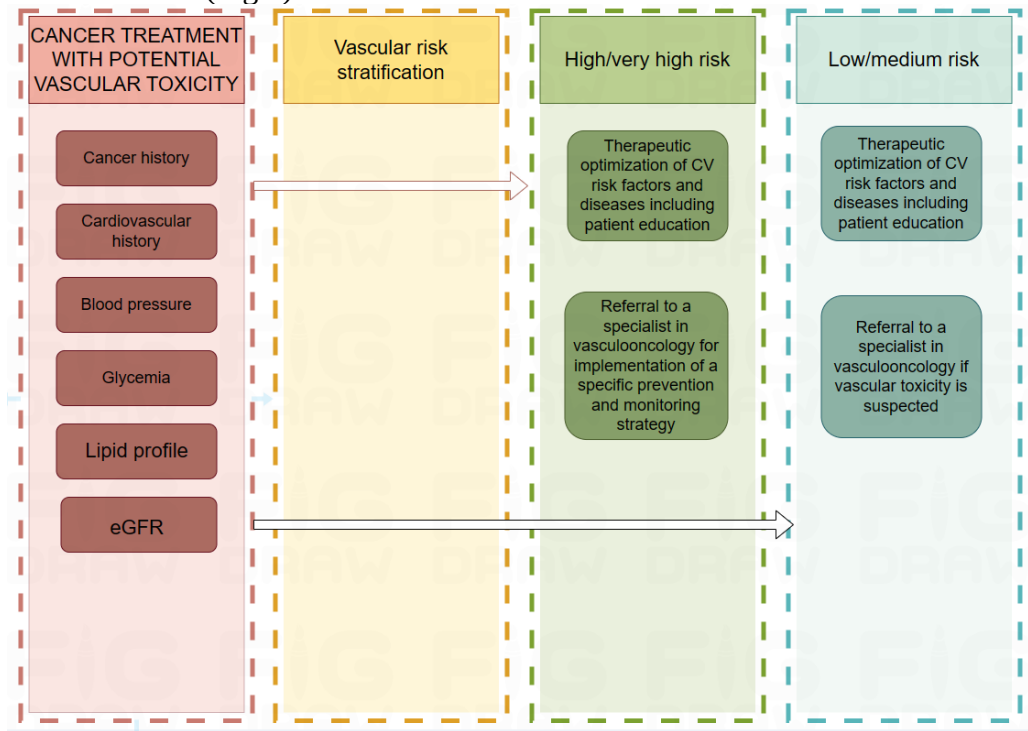


Fig. 3 A global pragmatic approach has been put forward to monitor the cardiovascular health of patients who are given cancer treatments with potential vascular toxicity [1].

Based on the management methods outlined by Concetta Zito et al., this article will list solutions for myocarditis, pericardial disease, infarction, arrhythmias and conduction disorders, and takotsubo-like cardiomyopathy [10] (Fig. 4).

	Myocarditis	Pericardial disease	Takotsubo syndrome	Acute coronary syndrome
Clinical Presentation	Shortness of breath Chest pain Pulmonary edema Cardiogenic shock	Shortness of breath Chest pain Cardiogenic shock (in cardiac tamponade)	Chest pain Shortness of breath Palpitation Pulmonary edema Cardiogenic shock	Chest pain Shortness of breath Cardiogenic shock
Diagnosis	Troponin NT-proBNP ECG Echocardiography CMR imaging	ECG Echocardiography CMR imaging (to evaluate concomitant myocarditis)	Troponin, NT-proBNP ECG Echocardiography CMR imaging Exclusion of ACS according to ESC and AHA guidelines	Troponin, NT-proBNP ECG Echocardiography Diagnostic algorithm according to ESC and AHA guidelines
Treatment	Discontinue ICI Immunosuppressive therapy (Methylprednisolone i.v. 500–1000 mg/day for 3–5 days, then switch to oral prednisone 1 mg/kg/day). If no response consider second-line immunosuppression Consider therapy for heart failure	Withhold ICI Immunosuppressive therapy (1 mg prednisone/kg/day) Consider NSAID and colchicine Pericardiocentesis if indicated Consider ICI rechallenge after recovery	Withhold ICI therapy No clear evidence on immunosuppressive therapy Follow management algorithm of Heart Failure Association position statement Avoid QT-prolonging drugs	Withhold ICI therapy No clear evidence on immunosuppressive therapy Treatment according to ESC and AHA guidelines - Consider ICI therapy rechallenge after > 30 days in stable patients

Fig. 4 Clinical manifestations, screening tools, and treatment strategies for four common diseases.

5. Summary

Immunotherapy is based on enhancing autoimmunity, based on the study of tumor immune evasion. ICIs, as a type of immunotherapy, should pay attention to their significant efficacy, but their toxicity and side effects should not be ignored, especially when used in patients with previous cardiovascular risk factors. It is essential to evaluate patients at each tumor stage of treatment. While the range of applications and indications for ICIs is gradually expanding, it should be noted that simply up-regulating the patient's immune response is not without harm. Common but non-fatal complications are more likely to be taken seriously by clinicians, but rare and fatal complications are more likely to result in clinical accidents, which are often overlooked because of their low incidence but have consequences that can seriously affect the prognosis. Therefore, early identification and management of potential dangers and mastering the balance between benefits and risks of ICIs will be one of the next important tasks in cancer science.

References

- [1] Meilhac A, Cautela J, Thuny F. Cancer Therapies and Vascular Toxicities. *Curr Treat Options Oncol*, 2022, 23(3): 333-47.
- [2] Wang J, Liu F, Li J, et al. Fruit and vegetable consumption, cardiovascular disease, and all-cause mortality in China. *Sci China Life Sci*, 2022, 65(1): 119-28.
- [3] Kottschade L A. Incidence and Management of Immune-Related Adverse Events in Patients Undergoing Treatment with Immune Checkpoint Inhibitors. *Curr Oncol Rep*, 2018, 20(3): 24.
- [4] Heinzerling L, Ascierto P A, Dummer R, et al. Adverse events 2.0-Let us get SERIOs: New reporting for adverse event outcomes needed in the era of immuno-oncology. *Eur J Cancer*, 2019, 112: 29-31.
- [5] Coustal C, Vanoverschelde J, Quantin X, et al. Prognosis of immune checkpoint inhibitors-induced myocarditis: a case series. *J Immunother Cancer*, 2023, 11(5).
- [6] Tan S, Day D, Nicholls S J, et al. Immune Checkpoint Inhibitor Therapy in Oncology: Current Uses and Future Directions: JACC: CardioOncology State-of-the-Art Review. *JACC CardioOncol*, 2022, 4(5): 579-97.
- [7] Nave O, Elbaz M, Bunimovich-Mendrazitsky S. Analysis of a breast cancer mathematical model by a new method to find an optimal protocol for HER2-positive cancer. *Biosystems*, 2020, 197: 104191.
- [8] Zhang Y, Zhang Z. The history and advances in cancer immunotherapy: understanding the characteristics of tumor-infiltrating immune cells and their therapeutic implications. *Cell Mol Immunol*, 2020, 17(8): 807-21.
- [9] Hu J R, Florido R, Lipson E J, et al. Cardiovascular toxicities associated with immune checkpoint inhibitors. *Cardiovasc Res*, 2019, 115(5): 854-68.
- [10] Wu Mengchao, Wu Zaid, Wu Zhaohan; edited by Chen Xiaoping, Wang Jianping, Zhao Jizong; associate edited by Qin Xinyu, Liu Yucun, Zhang Yingze, Sun Yinghao, Li Zongfang. *Surgery* 9th edition. Beijing: People's Health Publishing House, 2018.