Systemic Review on Cardiotoxicity in the Era of Immuno-Oncology

Mr. Vaibhav Manikrao Hiwale[1], Mr. Kuldeep Sukhdeo Kanadje[2], Dr. D. K. Vir[3], Mr. Abhishek Raosaheb Ghule[4], Mr. Hemant Machhindra Kakde[5], Mahesh Gajanan Farkade[6], Vaibhav Ramesh Gorade[7]

Pharmacy Department Shree Goraksha College of Pharmacy and Research Center, Khamgaon, Chh. Sambhajinagar, India

Abstract: The advent of immuno-oncology (IO) has revolutionized cancer treatment, particularly with the introduction of immune checkpoint inhibitors (ICIs) like anti-PD-1, anti-PD-L1, and anti-CTLA-4 therapies. These agents have demonstrated remarkable efficacy in various cancers by enhancing the immune system's ability to detect and destroy tumor cells. However, along with their clinical benefits, ICIs have introduced a range of immune-related adverse events (irAEs), among which cardiotoxicity, though rare, has emerged as a significant concern. Cardiotoxicity in the context of IO therapies includes myocarditis, pericarditis, heart failure, and arrhythmias. Myocarditis, in particular, can present with high morbidity and mortality, necessitating early recognition and intervention. The underlying mechanism is believed to involve immune-mediated inflammation of cardiac tissues, likely due to the overlap between tumor-associated antigens and self-antigens, leading to off-target effects on the myocardium. The incidence of cardiotoxicity with IO therapies is relatively low compared to other irAEs but can be life-threatening when it occurs. Studies suggest that patients with preexisting cardiovascular conditions may be at higher risk, and thus, the role of cardio-oncology has become pivotal in managing such patients. Emerging strategies to mitigate these risks include vigilant cardiovascular monitoring, the use of corticosteroids to manage inflammation, and collaborations between oncologists and cardiologists to ensure comprehensive care. As immuno-oncology continues to evolve, understanding and managing the risks of cardiotoxicity is crucial for optimizing patient outcomes. This review highlights the mechanisms, clinical manifestations, and management strategies of cardiotoxicity associated with immuno-oncology treatments, underscoring the need for further research to develop predictive biomarkers and safer therapeutic approaches.

Keywords: Arrhythmia; Cancer immunotherapy; Cardiotoxicity; Cardiovascular toxicity; Immune system; Myocarditis.

1. INTRODUCTION

The side effects of chemotherapy, particularly cardiovascular disease, have drawn a lot of attention due to the longer life expectancy of cancer patients nowadays. In fact, the frequency of cardiovascular events like heart damage, toxicity, or hypersensitivity is greater than the rate at which malignant tumors return [1]. The link between immunotherapy and cardiovascular risks calls for more research into underlying mechanisms. Combining ICIs with immune activators offers promise but poses challenges, especially after heart damage. Traditional treatments like anthracyclines may aid immunity but heighten heart risks. Insights into inflammation and clonal hematopoiesis are promising, though the CANTOS trial highlights hurdles in clinical translation despite positive results [2]. Recent oncology research has significantly enhanced our understanding of tumor growth, resistance, metastasis, and immune suppression. This has led to the development of many new compounds, with several promising agents awaiting approval. Immunotherapy is currently one of the most promising treatments for systemic cancer [3]. Oncologic treatments focus not only on efficacy but also on drug-related adverse reactions. While cancer therapies can affect multiple organ systems, cardiovascular side effects are particularly serious due to their impact on prognosis and quality of life. The cardiotoxicity of treatments like radiation and anthracyclines is well-documented [4]. Early detection of drug-related cardiotoxicity is crucial due to improved cancer survival. Type 2 cardiotoxicity, linked to drugs like trastuzumab, can reverse, while Type 1, from anthracyclines, causes permanent damage. Speckle-tracking (STE) and 3D echocardiography (3DE) are more accurate than traditional 2D echocardiography for detecting early heart changes. STE's global longitudinal strain (GLS) is especially useful in identifying subclinical damage, though it requires advanced imaging technology [5]. Radiation therapy or chemotherapy can lead to cardiovascular dysfunction. A recent study found that for left-sided breast cancer patients, the risk of ischemic heart disease increased by 6.2% per gray (Gy) of radiation dose, with a hazard ratio of 1.062 [6].

Key cardiovascular risk factors include hyperlipidemia, chronic renal disease, and aging. A left ventricle radiation dose (LV V25) > 4% is a stronger predictor of myocardial ischemia than the mean heart dose. While this may improve heart protection in breast cancer treatment, more research is needed. Radiation therapy can lead to acute events like heart attack and arrhythmias, and long-term issues such as heart failure and cardiomyopathy. Drugs may increase heart disease risk through blood pressure or direct cardiomyopathy effects [7].

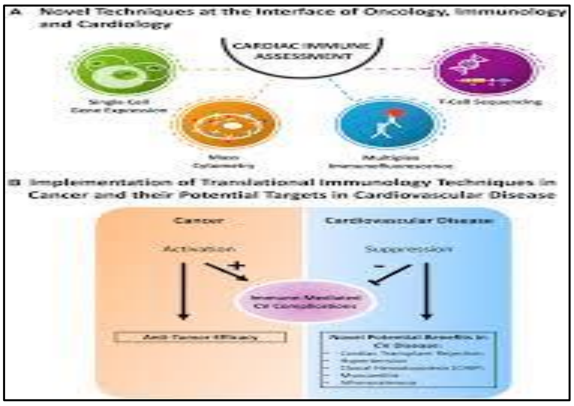

Fig. 1. The world of cardio-immunooncology.[2]

2. CARDIO TOXICITY

"Cardiotoxicity" in cancer treatment refers to a dose-dependent, lasting cardiovascular reaction that persists even after treatment stops. Unlike acute toxicity, which results from brief exposure, cardiotoxicity leads to a fibrotic response that requires histological confirmation, though this has been underexplored [8]. The terms "cardiac dysfunction related to cancer treatment" and "cardiotoxicity" are often used interchangeably, but there is disagreement on their definition, especially regarding chemotherapy. "Cardiotoxicity" is less commonly used for short-term side effects of monoclonal antibodies. Factors like exposure degree and route influence adverse effects, with chronic toxicity causing long-term harm and sub-chronic toxicity lasting over a year but less than a lifetime. Most definitions of cardiotoxicity focus on a progressive decline in left ventricular ejection fraction [9].

3. ICI-RELATED CARDIOTOXICITY

Type of Cardiotoxicity	Median Onset	Most Common Symptoms	Diagnosis	Treatment
Myocarditis	65 days	Shortness of breath, palpitations, edema, and fatigue	NT-proBNP, troponin I, endomyocardial biopsy, and CMR	High-dose corticosteroids
Pericarditis	30 days	Shortness of breath, chest pain	ECG changes, CMR, pericardial effusion, and fluid analysis	Pericardiocentesis, NSAIDs, colchicine, and high-dose corticosteroids
Takotsubo cardiomyopathy	15 weeks to 8 months	Unknown	ECG changes, troponin and NT-proBNP	High-dose corticosteroids
Arrhythmias and conduction disorders	Unknown	Unknown	ECG changes	High-dose corticosteroids, supportive
Myocardial infarction	Unknown	Chest pain and shortness of breath	ECG changes, troponin, and others	Cardiac catheterization, supportive

Fig. 2. ICI-associated cardiotoxicities and their characteristics [10]

3.1. Myocarditis

T cells targeting both tumor and heart antigens may contribute to cardiotoxicity, though the mechanism remains unclear. While CTLA-4, PD-1, PD-L1, and LAG-3 protect the heart, inhibiting ICIs may increase heart vulnerability, potentially causing myocarditis [11-12].

3.2. Pericardial Disease

Pericardial illness can arise from the same pathogenetic pathway as is described for ICI-related myocarditis, namely ICI stimulated cytotoxic T cells [13].

3.3. Takotsubo-Like Cardiomyopathy

The exact mechanism of ICI-associated Takotsubo cardiomyopathy is unclear, but it appears non-inflammatory, unlike myocarditis or pericarditis. ICIs may directly cause acute multi-vessel coronary spasms or indirectly induce myocardial stunning through adrenergic stress from rapid catecholamine release [14-15].

3.4. Myocardial Infraction

Although various mechanisms for ICI-related MI are proposed, none are conclusive. PD1 inhibition may activate T cells, worsening atherosclerosis and potentially causing cardiac ischemia, as PD1 is elevated in plaque T cells [16]. Acute MI from ICIs may result from inflammation causing plaque rupture or from coronary spasm following PD1 inhibitor treatment, with systemic inflammation potentially contributing. Direct T-cell-mediated coronary vasculitis is also a possible, though undocumented, mechanism in the absence of atherosclerosis [17].

3.5. Arrhythmias and Conduction Disorder

Conduction of energy disorders and ventricular arrhythmias are believed to be mostly caused by inflammation, either systemically or locally in the ventricle or His-Purkinje system. Myocarditis, pericarditis, systemic inflammation, or subsequent to another irAE, like thyroiditis, can all cause atrial fibrillation [18].

4. RISK FACTOR

An international registry identifies independent risk factors for ICI-related cardiotoxicity, including combined ICI therapy, diabetes, obesity, and anti-CTLA-4 medication. The risk of myocarditis is five times higher with combination therapy compared to monotherapy. Other potential risk factors include autoimmune disorders and pre-existing cardiovascular conditions like MI, heart failure, and previous cancer treatments. T-cell-mediated reactions and systemic inflammation from ICI therapy may worsen heart failure in vulnerable individuals, though this remains theoretical. The European Society of Cardiology guidelines recommend categorizing patients as low- or high-risk based on these factors and adjusting surveillance accordingly. Further research is needed to better identify patients at risk for cardiovascular immune-related adverse events. [19]

5. TREATMENTS

5.1. Ipilimumab: The FDA approved ipilimumab, a CTLA-4 antibody, in 2011 for treating lung cancer, melanoma, and other cancers. Common side effects include fatigue, diarrhea, rash, and colitis, while severe immune-related adverse events (IRAEs) occur in less than 1% of patients. For mild side effects, treatment can be paused until recovery, but severe IRAEs usually require permanent discontinuation of the medication [20-21].

5.2. Pembrolizumab: In 2014, the FDA approved pembrolizumab, a PD-1 antibody, for treating various cancers, including triple-negative breast cancer, lung cancer, and melanoma. Unlike regular IgG antibodies, it doesn't cause antibody-dependent cellular cytotoxicity. Up to 70% of patients experience immune-related issues, which can be severe or fatal [22-23].

5.3. Nivolumab: FDA-approved in 2014, nivolumab treats cancers like non-small-cell lung cancer. It doesn't cause antibody-dependent cytotoxicity. Common side effects include fatigue, rash, itching, diarrhea, pain, and nausea. IRAEs can occur long after treatment due to prolonged PD-1 inhibition, with cardiac reactions affecting less than 1% of patients [24-25].

5.4. Atezolizumab: Atezolizumab, approved in 2016, treats cancers like triple-negative breast cancer. Myocarditis or pericarditis occurs in less than 1% of patients, and treatment is stopped if cardiotoxicity occurs. More cases may arise with increased use as a first-line treatment [26-27].

5.5. Durvalumab: Durvalumab, approved in 2017, treats non-small-cell lung cancer and urothelial carcinoma. Common side effects include fatigue and UTIs, while severe ones like colitis and hepatitis can be fatal. High-grade reactions may require prolonged treatment discontinuation [28-29].

6. CLINICAL MANIFESTATION OF ICI-ASSOCIATED CARDIAC TOXICITY

6.1. Myocarditis: Myocarditis is the main symptom of immunotherapy-related cardiotoxicity, with a high fatality rate, especially in combination ICI therapy, where rates can exceed 76%. Prevalence has increased from 0.09% to 1-2%. Common symptoms include chest pain, fatigue, dyspnea, palpitations, and sudden cardiac death, often occurring within the first three months. Risk factors include combination therapies, prior cardiotoxic treatments, and pre-existing cardiovascular conditions. Diagnosis involves elevated cardiac biomarkers, ECG abnormalities, and imaging techniques like cardiac MRI (cMRI) and endomyocardial biopsy (EMB), with EMB being the gold standard. Prompt treatment is critical for better outcomes [30].

	Definite Myocarditis	Probable Myocarditis	Possible Myocarditis
based on emb pathology	tissue pathology consistent with myocarditis	not applicable	not applicable
		OR	
Based on cMRI	Diagnostic cMRI and clinical symptoms with at least one of: - positive biomarkers, - ECG abnormalities.	Diagnostic cMRI without any of the following: - clinical symptoms, - positive biomarkers, - ECG abnormalities. Suggestive cMRI with at least one of: - clinical symptoms, - ECG abnormalities, - positive biomarkers.	Suggestive cMRI without: - clinical symptoms, - ECG abnormalities, - positive biomarkers.
		OR	
Based on TTE	TTE with new WMA and all of the following: - clinical symptoms, - positive biomarkers, - ECG abnormalities, - negative angiography for CAD.	TTE with new WMA, clinical symptoms with at least one of the following: - ECG abnormalities, - positive biomarkers.	TTE with new WMA with at least one of: - clinical symptoms, - ECG abnormalities.
		OR	
Based on PET	not applicable	PET imaging showing patchy cardiac 18F-FDG uptake with clinical symptoms	not applicable
		OR	
Based on biomarkers	not applicable	not applicable	Elevated biomarkers, no alternative diagnosis with at least one of: - clinical symptoms, - ECG abnormalities.

Fig. 4. Proposed Classification of Myocarditis: Definite, Probable, and Possible [30]

6.2. Pericarditis: Pericarditis is the second most common ICI-related cardiotoxicity, often presenting as pericardial effusion or cardiac tamponade, and is more common in men. It typically occurs around 30 days after ICI therapy. Transthoracic echocardiography is essential for diagnosis, with cMRI and PET/CT aiding in peri myocarditis detection. Elevated troponin and ECG changes like tachycardia and ST elevation are common. Patients with malignant visceral involvement require close monitoring for rapid exudate buildup, as seen in lung cancer patients on nivolumab [31-32].

6.3. Arrhythmias: Atrial fibrillation (30%) is the most common arrhythmia caused by ICIs, followed by ventricular tachycardia (27%) and conduction abnormalities (17%). These abnormalities increase heart disease mortality significantly. Causes include inflammation, electrolyte imbalances, and systemic issues. Early ECG monitoring is essential for timely diagnosis and prevention of heart block [33-34]

7. DIAGNOSIS OF ICI-ASSOCIATED CARDIOTOXICITY

Repetitive ECGs and laboratory testing (such as cardiac troponin and natriuretic peptides) are recommended for the early detection of subclinical cardiotoxicity linked to ICI, together with quick access to TTE in questionable situations. A thorough physical examination and questions concerning heart symptoms should be asked at every visit during ICI treatment.

7.1. Electrocardiogram: Transthoracic echocardiography is key for diagnosing pericardial issues like tamponade and effusion. cMRI and PET/CT help diagnose peri myocarditis. Elevated troponin levels are common in peri myocarditis, and ECG may show tachycardia and ST-segment changes. Close monitoring is recommended for patients with malignant involvement, as seen in two lung cancer cases who developed cardiac tamponade after nivolumab. [35]

7.2. Imaging Techniques: TTE can detect pericardial effusion, WMA, LV changes resembling Takotsubo syndrome, and LV dysfunction. GLS should be assessed alongside LVEF to evaluate LV systolic function. Awadalla et al. found that patients with ICI-associated myocarditis had worse GLS, regardless of LVEF changes [50].

7.3. Laboratory Test: Transthoracic echocardiography is key for diagnosing pericardial disorders. cMRI and 18F-FDGPET/CT help diagnose peri myocarditis. Elevated troponin levels are common, and ECG may show tachycardia and ST-segment elevation. Patients with malignant visceral involvement should be monitored closely, as seen in two lung cancer patients who developed cardiac tamponade after nivolumab treatment. [30]

8. CLINICAL OUTCOME

Collaboration between immunologists, oncologists, and cardiologists is essential to address the growing concern of ICI-related cardiotoxicity, particularly in NSCLC patients. While myocarditis, especially in its fulminant form, is linked to poor outcomes, ICIs offer significant survival benefits. A meta-analysis by Rahouma et al. found that anti-PD/PD-L1 therapies did not significantly increase cardiotoxicity compared to chemotherapy. ICIs often result in better response rates, survival, and progression-free survival. Ongoing research is needed to identify risk factors and improve monitoring to optimize ICI benefits while minimizing cardiac risks. [30]

9. CARDIOVASCULAR HYPERSENSITIVITY

Cardiovascular hypersensitivity, a complex inflammation not dependent on dosage, can occur at any stage of chemotherapy or monoclonal antibody treatment. It is often linked to anti-drug antibodies like IgE and IgG and elevated tryptase levels. Diagnosing severe hypersensitivity, such as anaphylaxis, can be difficult without typical skin symptoms. The peak tryptase level must be at least 1-2 times the baseline plus 2 mg/L. Severe hypersensitivity may cause hypotension due to reduced cardiac output, plasma leakage, and decreased venous return.

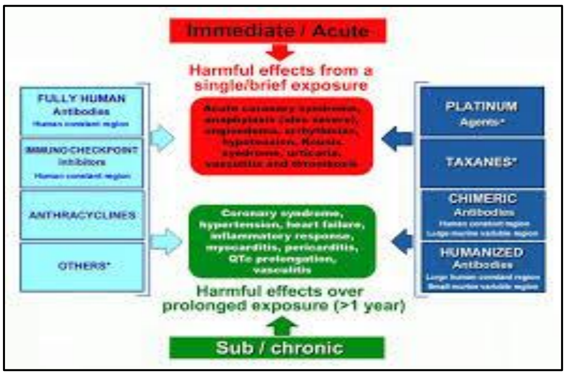

Fig. 5. Hypersensitivity (immune-allergic) responses to cancer therapeutic agents. [37]

Transthoracic echocardiography is key for diagnosing pericardial disorders, while cMRI and PET/CT help diagnose perimyocarditis. Elevated troponin levels and specific ECG changes, like tachycardia and ST-segment elevation, are common. Patients with malignant visceral involvement, especially those on nivolumab, should be closely monitored for rapid exudate buildup, as seen in two lung cancer cases. [37]

10. MECHANISM OF CARDIOVASCULAR TOXICITY

Transthoracic echocardiography is key for diagnosing pericardial disorders, while cMRI and 18F-FDGPET/CT help with peri myocarditis. Elevated serum troponin and ECG changes, like tachycardia and ST-segment elevation, are common in peri myocarditis. Patients with malignant involvement should be closely monitored, as rapid exudate buildup can occur, as seen in two lung cancer patients with cardiac tamponade after nivolumab. [38]

10.1. Anthracycline: The first type of chemotherapy-induced cardiotoxicity to be documented was anthracycline-induced cardiomyopathy. As a result, the mechanism has been studied the most and reflects the wide range of effects and toxicities of conventional chemotherapeutic drugs. This kind of cardiotoxicity, which has historically been known as type I, results in the death of cardiomyocytes. [39-40]
Transthoracic echocardiography is key for diagnosing pericardial disorders. cMRI and 18F-FDGPET/CT help diagnose peri myocarditis. Elevated troponin levels and ECG changes like tachycardia and ST-segment elevation are common. Close monitoring is recommended for patients with malignant visceral involvement, as seen in two lung cancer cases with cardiac tamponade after nivolumab. [41-42]

10.2. HER2/ErbB2 Inhibitor: Anthracyclines have long been the focus of studies on cardiac toxicity in cancer therapy. However, the introduction of trastuzumab, a HER2-targeting monoclonal antibody for HER2-positive breast cancer, has highlighted a different but related form of cardiac toxicity. [43]
Transthoracic echocardiography is key for diagnosing pericardial disorders, with cMRI and 18F-FDGPET/CT aiding in peri myocarditis diagnosis. Elevated troponin levels and specific ECG changes are common in peri myocarditis. Close monitoring is crucial for patients with malignant involvement, as seen in two lung cancer patients who developed cardiac tamponade after nivolumab. [44-45]

10.3. Immune Checkpoint Inhibitor: Immunological checkpoint inhibitors, like ipilimumab and nivolumab, have shown great promise in treating cancers such as metastatic melanoma. However, their use is associated with autoimmune side effects. [46-47] Checkpoint blocking agents make patients more susceptible to attacks on healthy tissue by enabling the immune system to become more active against cancerous cells. This can result in allergic consequences such adrenal insufficiency, pneumonitis, and hepatitis. [48-49]

11. CARDIOPROTECTIVE DRUGS

11.1. Dexrazoxane:

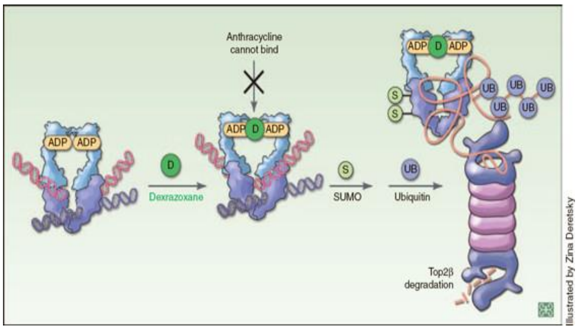

Fig. 6. Mechanisms of Dexrazoxane [64]

Transthoracic echocardiography is key for diagnosing pericardial disorders like tamponade, while cMRI and 18F-FDGPET/CT aid in diagnosing peri myocarditis. Elevated troponin levels and ECG changes like tachycardia and ST-segment elevation are common in peri myocarditis. Close monitoring is recommended for patients with malignancies, as seen in two lung cancer cases that developed cardiac tamponade after nivolumab treatment. [54-55]

11.2. β-blockers: Transthoracic echocardiography is key for diagnosing pericardial disorders, with cMRI and 18F-FDGPET/CT aiding peri myocarditis diagnosis. Elevated troponin levels and ECG changes, such as tachycardia and ST-segment elevation, are common. Patients with malignancies, especially lung cancer, should be closely monitored for rapid exudate buildup, as seen in two cases after nivolumab. [56-58]

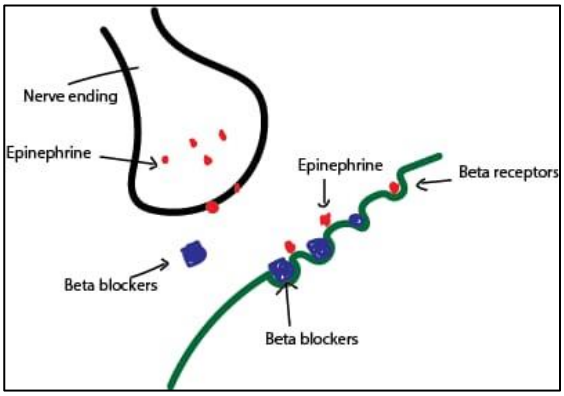

Fig. 7. Mechanisms of β-blockers [57]

11.3. Angiotensin converting-enzyme (ACE) Inhibitor Therapy (ACEIs): ACE inhibitors (ACEIs) may help prevent heart failure in patients at risk, such as those receiving chemotherapy. Studies show ACEIs protect against anthracycline-induced cardiomyopathy by influencing the heart's renin-angiotensin system, improving mitochondrial metabolism, reducing cardiac fibrosis, lowering cell apoptosis, and offering antioxidant effects. [59-61]

11.4. Neuregulin-1 (NRG-1): Transthoracic echocardiography is key for diagnosing pericardial disorders, with cMRI and PET/CT aiding in peri myocarditis diagnosis. Elevated troponin levels and ECG changes like tachycardia and ST-segment elevation are common in peri myocarditis. Patients with malignant visceral involvement, like those with lung cancer on nivolumab, should be closely monitored for rapid exudate development. [63]

12. DISCUSSION

The incorporation of immunotherapy into oncologic treatment regimens has yielded substantial enhancements in patient outcomes in recent years. However, this advancement comes with challenges, particularly regarding cardiotoxicity. Cardiotoxicity refers to the heart-damaging effects of certain cancer therapies, which can lead to heart failure and other cardiovascular complications. Immunotherapies, especially checkpoint inhibitors, have been associated with immune-related adverse events affecting the cardiovascular system. Identifying high-risk patients, such as those with pre-existing conditions, is crucial for effective monitoring and management. A collaborative, multidisciplinary approach involving oncologists, cardiologists, and other relevant specialists is crucial for mitigating cardiotoxicity risks. Continued research is essential to elucidate the underlying mechanisms of cardiotoxicity and to inform the development of targeted prevention and intervention strategies.

13. CONCLUSION

Immunotherapy has transformed cancer treatment, leading to better survival outcomes and providing new hope for numerous patients. However, a significant challenge is the risk of cardiotoxicity, which can lead to heart damage through immune-related adverse events. Understanding the mechanisms of cardiotoxicity is essential, especially for patients with pre-existing cardiovascular conditions or those receiving combination therapies. A proactive, multidisciplinary approach involving oncologists, cardiologists, and primary care providers is crucial for early identification and management, including regular cardiovascular monitoring.

REFERENCES

[1]. Wang, Y.; Wang, Y.; Han, X.; Sun, J.; Li, C.; Adhikari, B.K.; Zhang, J.; Miao, X.; Chen, Z. Cardio-Oncology: A Myriad of Relationships between Cardiovascular Disease and Cancer. Front. Cardiovasc. Med. 2022, 9, 727487.

[2]. Vlad G. Zaha, MD, PhD Wouter C. Meijers, MD, PhD Javid Moslehi, MD. Cardio-Immuno-Oncology. Circulation. 2020; 141:87–89. DOI: 10.1161/CIRCULATIONAHA.119.042276.

[3]. A.D. Waldman, J.M. Fritz, M.J. Lenardo, A guide to cancer immunotherapy: from T-cell basic science to clinical practice, Nat. Rev. Immunol. (2020) https://doi.org/10.1038/s41577-020-0306-5.

[4]. Y. Saleh, O. Abdelkarim, K. Herzallah, G.S. Abela, Anthracycline-induced cardiotoxicity: mechanisms of action, incidence, risk factors, prevention, and treatment, Heart Fail. Rev. (2020) https://doi.org/10.1007/s10741-020-09968-2.

[5]. Chun-Li Wang and Pao-Hsien Chu. Echocardiography for Evaluation of Oncology Therapy-Related Cardiotoxicity. Acta Cardiol Sin 2016; 32:560 564. doi: 10.6515/ACS20151024A.

[6]. Lai, T.Y.; Hu, Y.W.; Wang, T.H.; Chen, J.P.; Shiau, C.Y.; Huang, P.I.; Lai, I.C.; Tseng, L.M.; Huang, N.; Liu, C.J. Association of radiation dose to cardiac substructures with major ischemic events following breast cancer

radiotherapy. Eur. Heart J. 2023, 44,4796–4807.

[7]. Morelli, M.B.; Bongiovanni, C.; Da Pra, S.; Miano, C.; Sacchi, F.; Laurinol, M.; D'Uva, G. Cardiotoxicity of Anticancer Drugs: Molecular Mechanisms and Strategies for Cardio protection. Front. Cardiovasc. Med. 2022, 9, 847012.

[8]. Terada, C.I.; Onoue, K.; Fujii, T.; Itami, H.; Morita, K.; Uchiyama, T.; Takeda, M.; Nakagawa, H.; Nakano, T.; Baba, Y.; et al. Histopathological and epigenetic changes in myocardium associated with cancer therapy-related cardiac dysfunction. ESC Heart Fail. 2022, 9, 3031–3043.

[9]. He, Y.; Yu, H.; Dai, S.; He, M.; Ma, L.; Xu, Z.; Luo, F.; Wang, L. Immune checkpoint inhibitors break whose heart? Perspectives from cardio-immuno-oncology. Genes Dis. 2023, 11, 807–818.

[10]. Walid Shalata, Sarah Weissmann, et al. A Retrospective, Single-Institution Experience of Bullous Pemphigoid as an Adverse Effect of Immune Checkpoint Inhibitors. November 2022. 14(21):5451. DOI:10.3390/cancers14215451.

[11]. Durham, N.M.; Nirschl, C.J.; Jackson, C.M.; Elias, J.; Kochel, C.M.; Anders, R.A.; Drake, C.G. Lymphocyte Activation Gene 3(LAG-3) modulates the ability of CD4 T-cells to be suppressed in vivo. PLoS ONE 2014, 9, e109080.

[12]. Love, V.A.; Grabie, N.; Duramad, P.; Stavrakis, G.; Sharpe, A.; Lichtman, A. CTLA-4 ablation and interleukin-12 driven differentiation synergistically augment cardiac pathogenicity of cytotoxic T lymphocytes. Circ. Res. 2007, 101, 248–257.

[13]. Chen, D.Y.; Huang, W.K.; Chien-Chia Wu, V.; Chang, W.C.; Chen, J.S.; Chuang, C.K.; Chu, P.H. Cardiovascular toxicity of immune checkpoint inhibitors in cancer patients: A review when cardiology meets immuno-oncology. J. Formos. Med. Assoc. 2020, 119,1461–1475.

[14]. Lyon, A.R.; Yousaf, N.; Battisti, N.M.L.; Moslehi, J.; Larkin, J. Immune checkpoint inhibitors and cardiovascular toxicity. Lancet Oncol. 2018, 19, e447–e458.

[15]. Lyon, A.R.; Bossone, E.; Schneider, B.; Sechtem, U.; Citro, R.; Underwood, S.R.; Sheppard, M.N.; Figtree, G.A.; Parodi, G.;Akashi, Y.J.; et al. Current state of knowledge on Takotsubo syndrome: A Position Statement from the Taskforce on Takotsubo Syndrome of the Heart Failure Association of the European Society of Cardiology. Eur. J. Heart Fail. 2016, 18, 8–27.

[16]. Fernandez, D.M.; Rahman, A.H.; Fernandez, N.F.; Chudnovskiy, A.; Amir, E.D.; Amadori, L.; Khan, N.S.; Wong, C.K.; Shamailova, R.;Hill, C.A.; et al. Single-cell immune landscape of human atherosclerotic plaques. Nat. Med. 2019, 25, 1576–1588.

[17]. Nykl, R.; Fischer, O.; Vykoupil, K.; Taborsky, M. A unique reason for coronary spasm causing temporary ST elevation myocardial infarction (inferior STEMI)—Systemic inflammatory response syndrome after use of pembrolizumab. Arch. Med. Sci. Atheroscler.Dis. 2017, 2, e100–e102.

[18]. Salem, J.E.; Manouchehri, A.; Moey, M.; Lebrun-Vignes, B.; Bastarache, L.; Pariente, A.; Gobert, A.; Spano, J.P.; Balko, J.M; Bonaca, M.P.; et al. Cardiovascular toxicities associated with immune checkpoint inhibitors: An observational, retrospective, pharmacovigilance study. Lancet Oncol. 2018, 19, 1579–1589.

[19]. Concetta Zito, Roberta Manganaro, Giuliana Ciappina. Cardiotoxicity Induced by Immune Checkpoint Inhibitors: What a Cardio-Oncology Team Should Know and Do. Cancers 2022, 14, 5403. https://doi.org/10.3390/cancers14215403.

[20]. FDA. Highlights of Prescribing Information: Ipilimumab. Available online: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125377s110lbl.pdf (accessed on 3 June 2021).

[21]. Dolladille, C.; Ederhy, S.; Sassier, M.; Cautela, J.; Thuny, F.; Cohen, A.A.; Fedrizzi, S.; Chrétien, B.; DA Silva, A.; Plane, A.-F.; et al.Immune Checkpoint Inhibitor Rechallenge After Immune-Related Adverse Events in Patients With Cancer. JAMA Oncol. 2020, 6,865–871.

[22]. Michot, J.; Bigenwald, C.; Champiat, S.; Collins, M.; Carbonnel, F.; Postel-Vinay, S.; Berdelou, A.; Varga, A.; Bahleda, R.; Hollebecque, A.; et al. Immune-related adverse events with immune checkpoint blockade: A comprehensive review. Eur. Cancer 2016, 54, 139–148.

[23]. FDA. Highlights of Prescribing Information: Pembrolizumab. Available online: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125514s096lbl.pdf (accessed on 3 June 2021).
[24]. FDA. Highlights of Prescribing Information: Nivolumab. Available online: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125554s090lbl.pdf (accessed on 3 June 2021).
[25]. Brahmer, J.R.; Drake, C.G.; Wollner, I.; Powderly, J.D.; Picus, J.; Sharfman, W.H.; Stankevich, E.; Stankevich, A.; Salay, T.M.;McMiller, T.L.; et al. Phase I study of single-agent anti-programmed death-1 (MDX-1106) in refractory solid tumors: Safety,clinical activity, pharmacodynamics, and immunologic correlates. J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. 2010, 28, 3167–3175.Available online: https://pubmed.ncbi.nlm.nih.gov/20516446/ (accessed on 7 June 2021).
[26]. FDA. Highlights of Prescribing Information: Atezolizumab. Available online: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761034s033s034s035s036s037s038lbl.pdf (accessed on 6 August 2021).
[27]. Liu, S.-Y.; Huang, W.-C.; Yeh, H.-I.; Ko, C.-C.; Shieh, H.-R.; Hung, C.-L.; Chen, T.-Y.; Chen, Y.-J. Sequential Blockade of PD-1 andPD-L1 Causes Fulminant Cardiotoxicity-From Case Report to Mouse Model Validation. Cancers 2019, 11, 580. Available online: https://pubmed.ncbi.nlm.nih.gov/31022941/ (accessed on 6 August 2021).
[28]. FDA. Highlights of Prescribing Information: Durvalumab. Available online: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761069s002lbl.pdf (accessed on 6 August 2021).
[29]. BC Cancer. Durvalumab. Available online: http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Durvalumab_monograph.pdf (accessed on 6 August 2021).
[30]. Grzegorz Slawinski, Anna Wrona. Immune Checkpoint Inhibitors and Cardiac Toxicity in Patients Treated for Non-Small Lung Cancer: A Review.Int. J. Mol. Sci. 2020, 21, 7195; doi:10.3390/ijms21197195.
[31]. Salem, J.E.; Manouchehri, A.; Moey, M.; Lebrun-Vignes, B.; Bastarache, L.; Pariente, A.; Gobert, A.; Spano, J.P.;Balko, J.M.; Bonaca, M.P.; et al. Cardiovascular toxicities associated with immune checkpoint inhibitors: An observational, retrospective, pharmacovigilance study. Lancet Oncol. 2018, 19, 1579–1589.
[32]. Kolla, B.C.; Patel, M.R. Recurrent pleural effusions and cardiac tamponade as possible manifestations of pseudo progression associated with nivolumab therapy—A report of two cases. J. Immunotherapy. Cancer 2016, 4,80.
[33]. Bonaca, M.P.; Olenchock, B.A.; Salem, J.E.; Wiviott, S.D.; Ederhy, S.; Cohen, A.; Stewart, G.C.; Choueiri, T.K.;Di Carli, M.; Allenbach, Y.; et al. Myocarditis in the Setting of Cancer Therapeutics: Proposed Case Definitions for Emerging Clinical Syndromes in Cardio-Oncology. Circulation 2019, 140, 80–91.
[34]. Lyon, A.R.; Yousaf, N.; Battisti, N.M.L.; Moslehi, J.; Larkin, J. Immune checkpoint inhibitors and cardiovascular toxicity. Lancet Oncol. 2018, 19, e447–e458.
[35]. Upadhrasta, S.; Elias, H.; Patel, K.; Zheng, L. Managing cardiotoxicity associated with immune checkpoint inhibitors. Chronic Dis. Transl. Med 2019, 5, 6–14.
[36]. Abdel-Rahman, O. Does a patient’s sex predict the efficacy of cancer immunotherapy? Lancet Oncol. 2018, 19,716–717.
[37]. Nicholas G. Kounis, Ming-Yow Hung. Cardio-Oncoimmunology: Cardiac Toxicity, Cardiovascular Hypersensitivity, and Kounis Syndrome. Life 2024, 14, 400.
[38]. Timothy M. Markman, Maurie Markman. Cardio-Oncology: mechanisms of cardiovascular toxicity. F1000Research 2018, 7(F1000 Faculty Rev):113.
[39]. Cardinale D, Colombo A, Lamantia G, et al.: Anthracycline-induced cardiomyopathy: clinical relevance and response to pharmacologic therapy.J Am Coll Cardiol. 2010; 55(3): 213–20.
[40]. Volkova M, Russell R 3rd: Anthracycline cardiotoxicity: prevalence, pathogenesis and treatment. Curr Cardiol Rev. 2011; 7(4): 214–20.
[41]. Hahn VS, Lenihan DJ, Ky B: Cancer therapy-induced cardiotoxicity: basic mechanisms and potential cardioprotective therapies. J Am Heart Assoc. 2014; 3(2): e000665.
[42]. Chen Z, Norris JY, Finck BN: Peroxisome proliferator-activated receptor-gamma

coactivator-1alpha (PGC-1alpha) stimulates VLDL assembly through activation of cell death-inducing DFFA-like effector B (CideB). J Biol Chem. 2010; 285(34): 25996–6004.
[43]. Maurea N, Coppola C, Ragone G, et al.: Women survive breast cancer but fall victim to heart failure: the shadows and lights of targeted therapy. J Cardiovasc Med (Hagerstown). 2010; 11(12): 861–8.
[44]. Bria E, Cuppone F, Milella M, et al.: Trastuzumab cardiotoxicity: biological hypotheses and clinical open issues. Expert Opin Biol Ther. 2008; 8(12): 1963–71.
[45]. Ozcelik C, Erdmann B, Pilz B, et al.: Conditional mutation of the ErbB2 (HER2) receptor in cardiomyocytes leads to dilated cardiomyopathy. Proc Natl Acad Sci U S A. 2002; 99(13): 8880–5.
[46]. Naidoo J, Page DB, Li BT, et al.: Toxicities of the anti-PD-1 and anti-PD-L1 immune checkpoint antibodies. Ann Oncol. 2015; 26(12): 2375–91.
[47]. Champiat S, Lambotte O, Barreau E, et al.: Management of immune checkpoint blockade dysimmune toxicities: a collaborative position paper.Ann Oncol. 2016; 27(4): 559–74.
[48]. Weber JS, Kähler KC, Hauschild A: Management of immune-related adverse events and kinetics of response with ipilimumab. J Clin Oncol. 2012; 30(21): 2691–7.
[49]. Nishino M, Giobbie-Hurder A, Hatabu H, et al.: Incidence of Programmed Cell Death 1 Inhibitor-Related Pneumonitis in Patients with Advanced Cancer: A Systematic Review and Meta-analysis. JAMA Oncol. 2016; 2(12): 1607–16.
[50]. Chu TF, Rupnick MA, Kerkela R, et al.: Cardiotoxicity associated with tyrosine kinase inhibitor sunitinib. Lancet. 2007; 370(9604): 2011–9.
[51]. Wu S, Chen JJ, Kudelka A, et al.: Incidence and risk of hypertension with sorafenib in patients with cancer: a systematic review and meta-analysis. Lancet Oncol. 2008; 9(12): 117–23.
[52]. Ghoreschi K, Laurence A, O'Shea JJ: Selectivity and therapeutic inhibition of kinases: to be or not to be? Nat Immunol. 2009; 10(4): 356–60.
[53]. Ozdoğru I. Anthracycline-induced cardiotoxicity. Turk Kardiyol Dern Ars. 2014;42(3):274–276.
[54]. Van Dalen EC, Michiels EM, Caron HN, Kremer LC. Different anthracycline derivates for reducing cardiotoxicity in cancer patients. Cochrane Database Syst Rev. 2010:CD005006. doi: 10.1002/14651858.CD005006.
[55]. Hensley ML, Hagerty KL, Kewalramani T, Green DM, Meropol NJ, Wasserman TH, et al. American Society of Clinical Oncology 2008 clinical practice guideline update: use of chemotherapy and radiation therapy protectants. J Clin Oncol. 2009; 27:127–145. doi: 10.1200/JCO.2008.17.2627.
[56]. Nohria A. β-Adrenergic blockade for anthracycline- and trastuzumab-induced cardiotoxicity: is prevention better than cure? Circ Heart Fail. 2013;6(3):358–361. doi: 10.1161/CIRCHEARTFAILURE.113.000267.
[57]. Oliveira PJ, Bjork JA, Santos MS, Leino RL, Froberg MK, Moreno AJ, et al. Carvedilol-mediated antioxidant protection against doxorubicin-induced cardiac mitochondrial toxicity. Toxicol Appl Pharmacol. 2004; 200:159–168. doi: 10.1016/j.taap.2004.04.005.
[58]. Erickson CE, Gul R, Blessing CP, Nguyen J, Liu T, Pulakat L, et al. The beta-blocker Nebivolol Is a GRK/beta-arrestin Biased Agonist. PLoS One. 2013;8(8): e71980. doi: 10.1371/journal.pone.0071980.
[59]. Vaynblat M, Shah HR, Bhaskaran D, Ramdev G, Davis WJ, 3rd, Cunningham JN, Jr, et al. Simultaneous angiotensin converting enzyme inhibition moderate's ventricular dysfunction caused by doxorubicin. Eur J Heart Fail. 2002; 4:583–586. doi: 10.1016/s1388-9842(02)00091-0.
[60]. Boucek RJ, Jr, Steele A, Miracle A, Atkinson J. Effects of angiotensin-converting enzyme inhibitor on delayed-onset doxorubicin-induced cardiotoxicity. Cardiovasc Toxicol. 2003; 3:319–329. doi: 10.1385/ct:3:4:319.
[61]. Cernecka H, Ochodnicka-Mackovicova K, Kucerova D, Kmecova J, Nemcekova V, Doka G, et al. Enalaprilat increases PPARbeta/delta expression, without influence on PPARalpha and PPARgamma, and modulate cardiac function in sub-acute model of daunorubicin-

induced cardiomyopathy. Eur J Pharmacol. 2013; 714:472–477. doi: 10.1016/j.ejphar.2013.06.040.

[62]. Horie T, 1, Ono K, Nishi H, Nagao K, Kinoshita M, Watanabe S, et al. Acute doxorubicin cardiotoxicity is associated with miR-146a-induced inhibition of the neuregulin-ErbB pathway. Cardiovasc Res. 2010;87(4):656–664. doi: 10.1093/cvr/cvq148.

[63]. Liu X, Gu X, Li Z, Li H, Chang J, Chen P, et al. Neuregulin-1/erbB-activation improves cardiac function and survival in models of ischemic, dilated, and viral cardiomyopathy. J Am Coll Cardiol. 2006;48(7):1438–1447. doi: 10.1016/j.jacc.2006.05.057.