

Myocarditis in Cancer Patients: A Review of an Emerging Problem in Cardio-Oncology

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Abstract

Patients with cancer have a multitude of etiological factors for developing myocarditis. Classical or conventional chemotherapy, radiation therapy, and, more recently, immunotherapy have all been described as possible etiologies of myocarditis. Furthermore, patients with cancer are immunosuppressed and more susceptible to bacterial and viral infections that can cause myocarditis. This narrative review addresses the many possible causes of myocarditis in patients with cancer. Particular emphasis will be given to immune checkpoint inhibitor (ICI)-induced myocarditis. ICI myocarditis generally affects male patients, over the age of 50, who are being treated for lung cancer, melanoma, or renal cell carcinoma and have multiple comorbidities. Clinical manifestations present early, with elevated troponin and electrocardiogram changes. The case fatality rate is high. Treatment consists of discontinuation of the offending ICI and corticosteroid therapy. Myocarditis due to cyclophosphamide, anthracyclines, 5-fluorouracil, cisplatin, carboplatin, proteasome inhibitors, immunomodulators, tyrosine kinase inhibitors, and radiation therapy will also be addressed.

Introduction

Cancer was recognized as a disease many centuries ago, and its annual incidence currently exceeds 140 new cases per 100,000 population in most developed and developing countries. The prevalence of cancer is highest in the Northern Hemisphere, but in most countries, there are more than 250 cases per 100,000 population. Complications, even infrequent ones, become more noticeable as survival increases and the disease becomes more prevalent.¹

Cancer treatment has evolved since the pioneering use of arsenicals in 1908, from the revolution of the discovery of anthracyclines in the late 1960s to the recent advent of

immunotherapy today.² Both radiation therapy and classical chemotherapy can cause myocarditis in patients at increased risk of cardiotoxicity. Immunotherapy has revived fear of myocarditis as an adverse effect, due to its high lethality despite the low incidence. However, the multiple possible etiologies of myocarditis in cancer patients cannot be overlooked.

As a rule, patients with cancer are immunosuppressed, a condition which is compounded by the frequent use of corticosteroids or other immunomodulators. Furthermore, these patients are beset by long-term central venous access, diagnostic and therapeutic procedures, and hospitalizations. All of these factors culminate in increased risk of viral and bacterial infections, with the potential for development of myocarditis of various infectious etiologies and a severe course.

The clinical importance of myocarditis in patients with cancer lies both in its high lethality and in the need to discontinue or postpone anticancer therapy. This article will review the main clinical scenarios in which a patient with cancer may develop myocarditis as a complication or comorbidity, as well as the leading etiologies of myocarditis in this context.

Myocarditis in the cancer patient

Immune checkpoint inhibitors

Immune checkpoints are molecules – generally membrane receptors – that either stimulate or inhibit immune cells, which includes regulating T-cell activation. Inhibitory immune checkpoints have been studied as a potential therapeutic target against some malignant tumors. Immune checkpoint inhibitors (ICI) are monoclonal antibodies that target regulatory receptors and thus increase T-cell activation in response to tumor cells. The traditional logic of cytotoxic chemotherapy is thus inverted, insofar as therapy produces an immune activation that results in tumor blockade. Several different receptors can be blocked simultaneously by specific antibodies.³

The ICIs used in clinical practice and associated with adverse cardiovascular effects target cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), programmed cell death protein 1 (PD-1), and programmed cell death ligand 1 (PD-L1).

In 2014, during the initial regulatory process for clinical approval of the first ICIs, adverse effects involving the neurological, endocrine, pulmonary, gastrointestinal and renal systems were observed.⁴ Rare cardiovascular effects were also seen, though most likely underreported according to a review by Hu et al.⁵ who analyzed 22 clinical trials of PD-1 and PD-L1

Keywords

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inhibitors; only one case of myocarditis was reported, and, in 10 studies enrolling 1784 patients, a cardiotoxicity rate of 0.7% was recorded.

A series of myocarditis cases attributable to ICI was subsequently published in 2016.⁶ Other isolated case reports and case series followed, as well as pharmacovigilance studies and multicenter registries that attested to adverse cardiovascular effects, warning particularly of the possibility of severe myocarditis. Other adverse cardiovascular effects have been described, including arrhythmias and conduction disorders; pericardial involvement; vasculitis and temporal arteritis; Takotsubo cardiomyopathy; and hypertension.⁷ More recently, special focus has been given to the acceleration of atherogenesis by ICIs, with an increase in atherosclerotic plaque and, consequently, a threefold risk of events such as myocardial infarction, myocardial revascularization, and ischemic stroke.⁸⁻¹¹

ICI myocarditis has peculiar clinical features and will thus receive special focus in this review article. In parallel, we will address the other etiologies of myocarditis in patients receiving cancer therapies.

Immune checkpoint inhibitor-induced myocarditis

Epidemiological aspects

When the first cases of myocarditis attributed to ICIs were described, it was presumed to be a very rare adverse effect. However, the publication of a growing number of case series, pharmacovigilance studies, and registries showed the actual incidence of ICI myocarditis to range from 0.39% to 2.1%.^{12,13} Cases of ICI myocarditis have been described in a very wide age range (from 20 to 90 years), with a male predominance.¹²

As monitoring and screening of patients on ICIs – with serial measurement of cardiac troponin (cTn), B-type natriuretic peptide (BNP), and echocardiography – increased, so did the reported incidence of myocarditis. A summary of the current literature on the incidence of ICI myocarditis, the timing of onset after starting immunotherapy, and the incidence of major adverse cardiovascular events (MACE) and mortality is given in Table 1.

A recent study published findings from a large registry of 5,518 cancer patients on ICI therapy.¹³ Of these, 691 (12.5%) experienced some form of cardiotoxicity. Among the various manifestations of cardiotoxicity, arrhythmias and conduction disorders were most common (9.3% of patients), followed by myocarditis in 2.1% – the highest incidence published to

date. Acute myocardial infarction occurred in 1.7% of patients. Pericarditis had an incidence of 1.2%, and cardiomyopathies, 0.9%. In this large registry, myocarditis was fatal in 47% of cases. MACE was associated with lower patient survival.

This registry¹³ can also be used to construct a profile of patients on ICI therapy. Mostly, they are male, over the age of 50, and being treated for lung cancer, melanoma, or renal-cell carcinoma. They also have several comorbidities, such as hypertension, diabetes mellitus, chronic obstructive pulmonary disease, liver disease, and peripheral vascular disease. In other words, a profile very similar to that of patients with heart disease, which places them at high cardiovascular risk.

As a rule, ICI myocarditis is an early complication, occurring approximately at the third infusion or between the first and second months of therapy. Nevertheless, some late-presenting cases have been reported.¹⁴

Etiology and pathophysiology

Most patients (84.9%) were on one ICI; the remaining 15.1% were receiving two or three inhibitors. The most commonly used ICIs were PD-1 inhibitors, such as pembrolizumab and nivolumab. Overall, there was no difference in risk of cardiotoxicity between PD-1 and PD-L1 inhibitors. However, data suggest that initiation of therapy with ipilimumab and pembrolizumab carries a higher risk of adverse cardiovascular effects than with other agents.¹³

The exact mechanism of myocardial injury by ICIs is unclear. Evidence suggests that antigens shared between tumor cells and myocardium elicit an immune response to both structures. This model resembles the known pathophysiology of viral myocarditis.¹⁴

Diagnosis, monitoring, and screening

The clinical import of ICI myocarditis lies in its high case fatality rate and potential for other major cardiovascular events. Case series have shown that 50% of patients with ICI myocarditis die. Therefore, even if the overall incidence is low, the high lethality of this complication should lead clinicians to seek diagnosis as early as possible, allowing rapid initiation of therapy. Thus, in addition to maintaining a high index of suspicion, clinicians should actively screen patients at risk.

Troponin I was elevated in 14.3% of all patients receiving ICIs, with elevation occurring around the 27th

Table 1 – Epidemiological and clinical features of immune checkpoint inhibitor-induced myocarditis

Authors	Year	Type of study	Incidence of myocarditis (%)	Mean/median time to onset (days)	MACE (%)	Case fatality (%)
Mahmood SS et al.	2018	Multicenter registry	1.14	34	46.0	-
Salem JE et al.	2018	Multicenter registry	0.39	30	-	50.0
Li C et al.	2022	Nationwide registry	2.10	115	-	47.0
Furukawa A et al.	2022	Single-center clinical trial	10.30	44	3.2	-

MACE: major adverse cardiovascular events (such as death, myocardial infarction, or stroke).

day after starting treatment. Troponin elevation was more frequent than elevation of BNP or creatine phosphokinase (CK-MB).¹⁵

Electrocardiography (ECG) showed several changes, while the echocardiogram was normal in most patients.¹⁵ The most frequent ECG changes on baseline examination of patients with ICI myocarditis are increased heart rate, prolongation of the QT interval (Fridericia-corrected), low voltage, left bundle branch block, and repolarization changes.¹⁶ The ECG also has prognostic value, as patients with ICI myocarditis with left bundle branch block, pathologic Q waves, or low voltage are at increased risk of overall mortality.¹⁶

Case series showed that almost all cases of ICI myocarditis (94%) had elevated troponins and an abnormal ECG (89%), while left ventricular ejection fraction (LVEF) by echocardiography was preserved in 51%. This differs markedly from the classic pattern of viral myocarditis, i.e., chamber enlargement and severe systolic dysfunction with reduced LVEF. This can be a confusing finding for the clinician. Therefore, ICI myocarditis should be suspected even in the presence of preserved LVEF.¹⁷

Some factors associated with ICI myocarditis have been speculated, including presence of diabetes mellitus, sleep apnea, and high body mass index.¹⁷

The Society for Immunotherapy of Cancer (SITC) has published a guideline that recommends the following:¹⁷

1. A diagnosis of ICI-induced myocarditis should be considered in any patient developing new cardiac symptoms, new cardiac arrhythmias, new heart blocks, or cardiac lab findings (e.g., asymptomatic troponin elevation) who has received an ICI therapy in the past 12 weeks. Suspicion of ICI-induced myocarditis should trigger hospital admittance and consultation with a cardiologist.
2. Patients with suspected ICI-induced myocarditis should undergo cardiac MRI if available (with or without right heart catheterization and myocardial biopsy), ECG, and testing for serum troponin levels.

The European Society of Cardiology made more aggressive recommendations in its Cardio-Oncology Guideline:¹⁸

1. ECG, NP, and cTn measurements are recommended in all patients before starting ICI therapy.
2. Baseline echocardiography is recommended in high-risk patients before starting ICI therapy.
3. Serial ECG and cTn measurements should be considered before ICI doses 2, 3, and 4, and if normal, reduce to every three doses until completion of therapy to detect subclinical ICI-related CV toxicity.
4. CV assessment is recommended every 6–12 months in high-risk patients who require long-term (>12 months) ICI treatment.

Patients with clinical suspicion of myocarditis due to ICI should proceed with diagnostic confirmation with cardiac magnetic resonance (CMR). Currently, specific CMR features for ICI-induced myocarditis are not well described and modified Lake Louise criteria are recommended.¹⁸

Endomyocardial biopsy (EMB) should be considered in cases where the diagnosis is suspected but not confirmed non-invasively (e.g., conflicting results of cardiac imaging and biomarkers or clinically unstable patients).¹⁸

Differential diagnosis

Studies have reported an increased incidence of atherosclerotic cardiovascular disease after ICI therapy, with a consequent higher occurrence of acute events such as myocardial infarction, ischemic stroke, and severe arterial disease.^{10,11} Therefore, when raising the diagnostic hypothesis of ICI myocarditis, acute coronary syndromes must be ruled out.

Other manifestations of ICI cardiotoxicity should be borne in mind, including malignant arrhythmias, pericardiopathies, and cardiomyopathies in general. Takotsubo cardiomyopathy must not be overlooked, as it is common in cancer patients regardless of the use of immunotherapy.¹³

Classification of myocarditis

The European Cardio-Oncology Guideline recommends that all cases of ICI-associated myocarditis should be classified according to severity as fulminant or non-fulminant. The treatment and follow-up algorithm should be adopted on the basis of this classification.¹⁸

Another group of authors has suggested classifying myocarditis as definite, probable, or possible, according to clinical, ECG, laboratory, imaging, and pathology findings.¹⁴

Treatment

Patients with suspected ICI-induced myocarditis who are clinically stable should receive high-dose corticosteroids (1000 mg methylprednisolone IV or equivalent) daily, for 3 to 5 days, until troponin levels are normal. This should be started as soon as possible once the diagnosis is considered likely/probable and should be followed by 4 to 6 weeks of oral prednisone at 1 to 2 mg/kg, tapering off slowly.¹⁸

There is a consensus that ICI therapy must be discontinued immediately in all cases of suspected ICI myocarditis, even if the diagnosis is not yet confirmed. In patients who had an unconfirmed suspicion of myocarditis, ICI treatment should only be restarted after discussion by a multidisciplinary team and a positive assessment of the risk-benefit ratio.¹⁸

Patients with fulminant myocarditis should be admitted to an intensive care unit for monitoring and circulatory support, with consideration of second-line immunosuppressive treatment as necessary.¹⁸

The therapeutic response should be monitored through serial ECG and troponin measurements.

There is no consensus regarding second-line immunosuppression. Caution is advised against the use of infliximab, as there have been recent reports of complications with this immunosuppressant.¹⁸

Other etiologies of myocarditis in the patient with cancer

Myocarditis secondary to cytotoxic therapies

A systematic review using World Health Organization (WHO) data investigated 5100 reported cases of drug-induced myocarditis between 1967 and 2020. The sample was divided into five classes of therapies: antipsychotics, immunotherapies, vaccines, salicylates, and cytotoxic drugs. Cytotoxic drugs – alkylating agents, anthracyclines, and antimetabolites – were implicated in 3.7% of cases, and were most frequently associated with heart failure and renal dysfunction. Women were slightly more affected, representing 52% of the sample, and the mortality rate was 24%, second only to that related to immunotherapies.¹⁹

Cyclophosphamide myocarditis

Cyclophosphamide is a nitrogen mustard-derived alkylating agent with potent antineoplastic, immunosuppressive, and immunomodulatory properties. Its use in cancer therapy and pre-hematopoietic stem cell transplant conditioning regimens is long established.²⁰

Cyclophosphamide is associated with acute myocarditis, often of a hemorrhagic, multifocal type. Cyclophosphamide metabolites cause direct and oxidative damage to the capillary endothelium, resulting in edema, interstitial hemorrhage, and microthrombus formation.²¹

Cardiomyopathy secondary to cyclophosphamide presents clinically with tachyarrhythmias, hypotension, heart failure, myocarditis, and pericardial involvement, generally occurring 2 to 10 days after an infusion. Hemorrhagic myocarditis is rare; however, once established, it progresses inexorably from acute heart failure to pericardial tamponade and cardiogenic shock, which is usually fatal. Patients on high-dose cyclophosphamide, older adults, or patients who have already received cardiotoxic therapies, such as anthracyclines or radiation to the chest, are at increased risk. The diagnosis of cyclophosphamide-associated myocarditis can be suspected by a resting ECG with increased QTc interval dispersion and by the echocardiographic findings of ventricular hypertrophy, a decrease in ejection fraction, and normal chamber size. CMR can confirm this diagnostic suspicion. Biomarkers can aid diagnosis by showing early elevations in BNP and troponin (Table 2).²⁰

A high index of suspicion is needed to achieve early diagnosis and implement the necessary therapeutic measures, which may include – in addition to the usual treatment of heart failure – pericardiocentesis if tamponade develops and, occasionally, ventricular assist devices as a bridge therapy.²⁰

Anthracycline-induced myocarditis

Myocarditis may be a rare manifestation of anthracycline cardiotoxicity. This complication is unrelated to the cumulative dose, is reversible in most cases, and allows re-exposure to the drug with judicious multidisciplinary follow-up. The mechanism of anthracycline toxicity is directly related to the oxidative stress resulting from their metabolism, in addition to inhibition of topoisomerase IIb, which ultimately result in damage to cardiomyocyte DNA.²¹ Among the

Table 2 – Proposed criteria for the early diagnosis of cyclophosphamide-associated hemorrhagic myocarditis

Necessary conditions for the diagnosis of hemorrhagic myocarditis (must be present)

1. Dose > 40 mg/kg/day or 1.4 mg/m²/day for 2 consecutive days
2. Heart failure symptom onset 3-12 days after infusion
3. Troponin elevation (peak at least 0.75 ng/dL) in the absence of anginal symptoms
4. Electrocardiogram with new diffuse low voltage

In addition to these, at least one additional imaging or other diagnostic modality demonstrating abnormalities would be required:

- Echocardiography: new pericardial effusion, increased intraventricular septal thickness during diastole, diastolic dysfunction, functional mitral regurgitation
- Cardiac MRI
- Myocardial biopsy: intramyocardial extravasation of blood, fibrin, or fibrin/platelet microthrombi in capillaries; fibrin strands in the interstitium

Source: Adapted from Wadia S, 2015.²²

anthracyclines, those most often associated with this condition are daunorubicin, epirubicin, and doxorubicin. Myocarditis often occurs in patients receiving more than one cancer therapy, and may also be related to additional mechanisms of cardiotoxicity.¹⁹

5-Fluorouracil (5-FU)-induced myocarditis

The most common manifestations of cardiotoxicity associated with fluoropyrimidines are angina pectoris and acute coronary syndromes. Other, less common manifestations include myocarditis and pericarditis, atrial fibrillation and other arrhythmias, heart failure, and even death.²³

Visible evidence of myocarditis was demonstrated in rabbits exposed to 5-fluorouracil (5-FU), with left ventricular hypertrophy, focal myocardial necrosis, thickening of intramyocardial arterioles, and disseminated apoptosis in myocardial and endothelial cells. In this study, administration of a single high dose of 5-FU was intended to distinguish the acute toxic effects of 5-FU, which resulted in thrombogenesis and spasm due to endothelial damage, from late cardiotoxicity after four injections at 7-day intervals, which led to apoptosis of myocardial and endothelial cells without evidence of spasm. These results support an alternative mechanism for 5-FU cardiotoxicity beyond vasomotor spasm and ischemia.²⁴

In humans, biventricular enlargement and diffuse necrosis with inflammatory infiltrates and proliferation of the sarcoplasmic reticulum with marked vacuolation have also been demonstrated, similar to those found in doxorubicin-induced cardiotoxicity. Such findings have been reported postmortem in patients treated with 5-FU. This condition may represent the consequences of any, all, or a combination of the pathological processes described above. Additional clinical evidence of a cardiomyopathic process was provided by studies that demonstrated echocardiographic evidence of left ventricular dysfunction and neuroendocrine changes,

characterized by elevated NP and lactic acid levels in the plasma of patients treated with 5-FU, even in the absence of significant changes in LVEF, thus suggesting a subclinical process.²⁴

Cisplatin and carboplatin myocarditis

Cisplatin has been widely used for the treatment of several types of cancer, including tumors of the head and neck, esophagus, lung, bladder, ovary, cervix, breast, testicle, penis, endometrium, and mesothelium, among others; in testicular cancer, it has made remission rates above 90% possible.²⁵

Accumulation of cisplatin in the renal proximal tubules and cardiac tissue results in activation of the redox-sensitive transcription factor nuclear factor kappa-B (NF- κ B), as well as of mitogen-activated protein kinase (MAPK). This process results in infiltration of immune cells, such as macrophages and neutrophils, and the production of proinflammatory cytokines, which combine to cause inflammation, cell death, and tissue damage.²⁵

There have been reports of myocarditis secondary to carboplatin-paclitaxel combination therapy in the treatment of thymoma²⁶ and secondary to carboplatin-pemetrexed therapy in patients with non-small cell lung cancer.²⁷

Myocarditis secondary to proteasome inhibitors and immunomodulators

Proteasome inhibitors, such as carfilzomib and bortezomib, and immunomodulators, such as lenalidomide, are used for the treatment of various hematologic malignancies, including multiple myeloma (MM), mantle cell lymphoma, systemic light-chain amyloidosis, T-cell lymphoma, and Waldenstrom macroglobulinemia/lymphoplasmacytic lymphoma, among others (Figure 1).²⁸

The proteasome plays an important role in maintaining cardiac protein homeostasis and protein quality in myocytes, preserving cell mass, and controlling sarcomere quality. Inhibition of proteasomal activity thus leads to a buildup of misfolded proteins, which can result in cell apoptosis, inflammation, and acute myopericarditis.²⁸

Eosinophilic myocarditis is a rare condition occurring secondary to treatment with lenalidomide. As the name implies, it results from an inflammatory process with eosinophil infiltration of the myocardium. The clinical presentation may range from a chronic restrictive cardiomyopathy to an acute fulminant myocarditis. It is usually associated with a pruritic rash, peripheral blood eosinophilia, and autoimmune manifestations such as thyroiditis, colitis, or pneumonitis. It may also involve cardiac symptoms such as heart failure and chest pain, with associated ECG changes and elevated troponin in the absence of myocardial ischemia.²⁹

Interestingly, as seen in Table 3, most of the reported cases have occurred in women who presented with myocarditis, usually in the first month of treatment.

Bruton's tyrosine kinase inhibitor-associated myocarditis

Bruton's tyrosine kinase inhibitors are widely used for the treatment of hematologic malignancies, such as

chronic lymphocytic leukemia, mantle cell lymphoma, and Waldenström macroglobulinemia, among others. The most commonly described adverse effects are high blood pressure, atrial fibrillation, and bleeding. There is also an established albeit less frequent association with heart failure and ventricular arrhythmias.³⁵

Some reports have also raised the possibility of myocarditis after initiation of therapy with Bruton's tyrosine kinase inhibitors. In an analysis of the WHO VigiBase database, among more than 13,000 patients receiving ibrutinib, two cases of myocarditis were reported as potential adverse effects. More recently, a case of acute eosinophilic myocarditis was reported after starting ibrutinib, with an inflammatory infiltrate generating an increase in septal thickness and abnormalities that mimicked those of cardiac amyloidosis.³⁶

A recent study reported that delayed myocardial enhancement on cardiac MRI was seen in 13.3% of patients before starting ibrutinib, versus 54.8% of patients on ibrutinib treatment. This study also showed a higher incidence of changes in native-T1 and max-T2 measures when comparing patients with and without ibrutinib exposure.³⁷

Radiation myocarditis

Cardiotoxicity is quite common after radiotherapy, especially when the precordium is irradiated with high doses and particularly when the left breast or chest is the target area. The main radiation therapy-associated cardiotoxicities are acute pericarditis, myocarditis, cardiac arrhythmias, myocardial dysfunction/heart failure, and myocardial ischemia.³⁸

In response to ionizing radiation exposure, there is a release of proinflammatory and profibrotic cytokines, such as tumor necrosis factor (TNF), interleukin (IL)-1, IL-6, IL-8, basic fibroblast growth factor (bFGF), insulin-like growth factor (IGF), connective tissue growth factor (CTGF), platelet-derived growth factor (PDGF), and transforming growth factor-beta (TGF- β 1). TGF- β 1 is known to be more closely associated with the development of tissue fibrosis; its functions include regulating cell growth and differentiation and promoting cell proliferation, inhibiting maintenance of the inflammatory response.³⁹

Diffuse myocardial fibrosis can occur after radiation doses greater than 25-30 Gy. Patients who have been irradiated on fields surrounding the heart are six times more likely to develop heart failure.⁴⁰

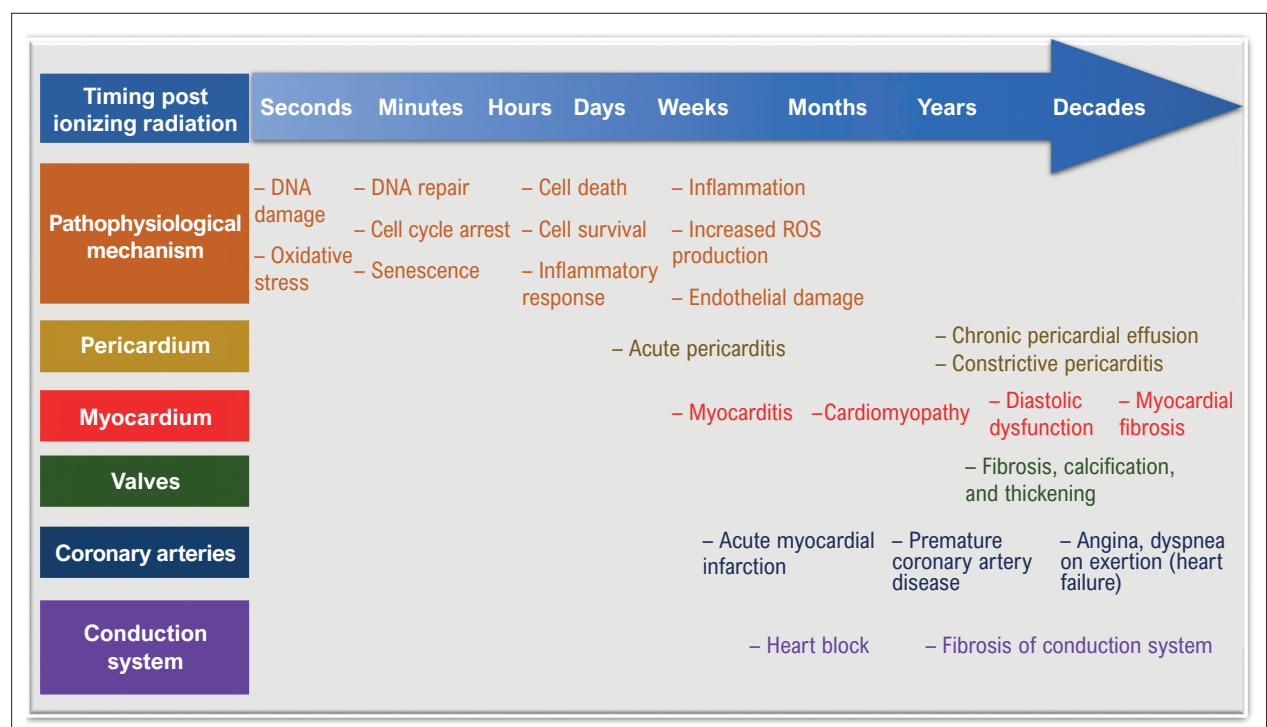
Acute radiation-induced myocarditis results from direct inflammation of the myocardium, and can be identified by reversible ECG changes and increases in plasma biomarkers such as C-reactive protein, troponin I, and CK-MB. Echocardiography, to measure systolic ejection fraction and global longitudinal strain (GLS), should be considered, as should CMR.⁴⁰

In one study, 6% of 1820 cancer survivors treated with anthracycline-containing chemotherapy ($n = 1050$), radiation ($n = 306$), or both ($n = 464$) had reduced ejection fraction on three-dimensional echocardiography ($< 50\%$). On GLS measurement, 32% of patients with a normal

Table 3 – Case reports of lenalidomide/bortezomib-associated myocarditis

Treatment regimen	Age (years)	Sex	Time to symptom onset (days)	Treatment	Outcome	Reference
Lenalidomide	85	F	17	Discontinuation of treatment + corticosteroids + supportive care	Fatal tachyarrhythmia	Carver Jr. et al., 2010 ³⁰
Lenalidomide/bortezomib	59	F	20	Discontinuation of treatment + corticosteroids + supportive care	20% ejection fraction; no further improvement after resolution	Sanchez-Petitto et al., 2020 ³¹
Lenalidomide/rituximab	66	F	30	Discontinuation of treatment + corticosteroids + supportive care	Full recovery	Jacob et al., 2020 ³²
Lenalidomide/rituximab	86	F	14	Supportive care	Clinically improved; transient decline in ejection fraction to 25%, improving to 55% after starting treatment for heart failure	Tse et al., 2021 ³³
Lenalidomide/bortezomib	69	F	19	Discontinuation of treatment + corticosteroids + supportive care	Clinically improved	Verbesselt et al., 2022 ²⁹
Lenalidomide/bortezomib	40	F	21	Temporary discontinuation of bortezomib + corticosteroids + supportive care	Clinically improved; treatment continued with lenalidomide alone	Alali et al., 2021 ²⁸
Lenalidomide/bortezomib	53	M	At the start of treatment	Temporary discontinuation of bortezomib + corticosteroids + supportive care	Clinically improved; treatment continued with lenalidomide alone	Cheney et al., 2019 ³⁴

Source: Own work. F: female; M: male.

**Figure 1 – Sequence of cardiovascular changes after exposure to ionizing radiation. Source: Adapted from Liu et al., 2022.³⁸**

ejection fraction had signs of systolic dysfunction, and 9% had signs of diastolic dysfunction.⁴¹

Other etiologies

In some scenarios, the causative agent of myocarditis is difficult to determine, as patients are being treated with multiple drugs or have a history of recent COVID-19 infection, COVID-19 vaccination, or infection with other viruses commonly associated with myocarditis.^{42,43}

Author Contributions

Conception and design of the research, Acquisition of data, Analysis and interpretation of the data, Writing of the manuscript and Critical revision of the manuscript for important intellectual content: Martins WA.

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