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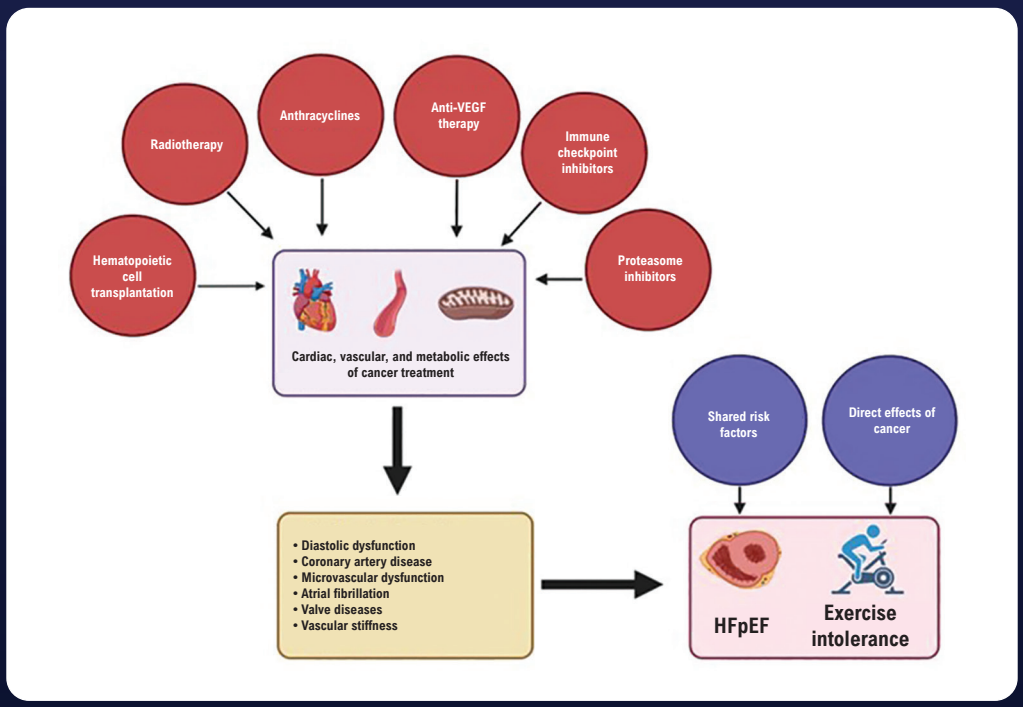

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Cardio-Oncology: Far Beyond Doxorubicin and the Tip of the Iceberg!

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Cardio-oncology is a new field of work and research on the adverse cardiovascular effects of cancer treatment, comorbidities and clinical conditions in cancer patients, and cardiovascular tumors. It has a wide spectrum ranging from arterial hypertension, arrhythmias, coronary and thromboembolic diseases to ventricular dysfunction, among others. In this special issue of ABC Heart Failure, we will focus on myocardial lesions, and consequently cardiomyopathies, ventricular dysfunction and heart failure (HF).

The Department of HF of the Brazilian Society of Cardiology has embraced Cardio-oncology since its beginning, by opening space for scientific discussion in its events and thematic area for abstract submissions, and now by offering this special issue addressing the main manifestations of endomyocardial/pericardial diseases and HF in cancer patients.

In these patients, cardiotoxicity used to be confused with left ventricular dysfunction and HF. Right after its discovery at the end of the 60s, higher and cumulative doses of anthracyclines were found to be associated with HF,[1,2] which was suggested by case reports. However, cardiotoxicity has remained unreported for a long time. The first works of oncology were not aimed at investigating cardiovascular adverse events, which were usually only reported when they became relevant clinical problems. HF is the severe, symptomatic, end-stage manifestation of myocardial injury. Thus, we only knew the visible tip of the iceberg.

With the speed required for the approval of new drugs in oncology, the methodological rigor has been neglected. The search for the cure of cancer has been considered more important to the detriment of potential adverse effects. Regulatory agencies have adopted a simplified system to approve new therapies in oncology. All contributed to keep clinical and subclinical manifestations of cardiotoxicity unnoticed by most people.

Scientific knowledge has increased *pari passu* with increasing publication of reports, from case reports, series, registries, pharmacovigilance studies to prospective, controlled, longitudinal studies. Anthracycline-induced ventricular dysfunction is current textbook knowledge; however, several other myocardial stressors have emerged. The old radiotherapy was revealed to be cardiotoxic, with late-onset lesions that are frequently associated with coronary, valve, pericardial and conduction system lesions. Other antineoplastic agents have joined the group of myocardial stressors, including cyclophosphamide-induced myocarditis, and ventricular dysfunction caused by the so-called "groundbreaking" target therapy, with the anti-HER2 monoclonal antibody, that revolutionized breast cancer treatment – the trastuzumab. Tyrosine kinase inhibitors, known as "oral chemotherapy", have been associated with hypertension, ventricular dysfunction, and HF with preserved ejection fraction. Immunotherapy, the fourth pilar of cancer treatment, has changed the paradigm as a new targeted treatment that strengthens patient's immune system, but with the side effect of an uncommon, difficult to be recognized, highly lethal myocarditis. Therefore, in cardio-oncology, many are the stressors to the myocardium and the villains.

We must face the multiple and eclectic challenges! Latin America is an example of a region with difficult access to the diagnosis and treatment of cancer.[3] We are far from achieving risk stratification of all patients diagnosed with cancer, which has been recently recommended by the European Society of Cardiology Guidelines on cardio-oncology.[4]

To know and early identify the mechanisms of myocardial lesion; stratify the risks; prevent; properly treat; rehab. The increase in the incidence of cancer and survival of the patients potentializes the increase in the prevalence.[5] There will be many patients and few qualified specialists. In parallel, we must share this new knowledge, in a didactic and strategic way under the epidemiological and clinical perspective. Brazil was the pioneer in publishing consensuses in the field,[6,7] and we need to rapidly democratize cardio-oncology, by means of articles, journals, events and courses.

Based on the exposed, cardio-oncology encompasses from the classical late-onset lesion caused by anthracycline in breast cancer patients to the acute myocarditis caused by immune checkpoint inhibitors and CART-T Tcells.[8] In this special issue of the ABC Heart Failure, we will address several clinical situations and clinical manifestations in the patient with cancer. For this purpose, we counted on the collaboration of some "explorers" in cardio-oncology in Brazil, enthusiasts and scholars who wrote the 19 articles of the issue. We thank the coauthors who kindly shared their time and knowledge. For readers, we hope this issue will be useful to help them navigating safely and finding out the exact dimension of the iceberg in front of us.

Keywords

Cardio-oncology; Chemotherapy/adverse effects; Oncology; Cardiology.

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Cardio-Protection Against Cancer Treatment-Related Cardiac Dysfunction: Who is at Risk?

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Long-term survival of cancer patients has improved, and the sequelae of treatment have become more evident. Mortality rates of cancer patients, adjusted for age, have decreased globally, with a reduction by 17% from 1990 to 2019.[1]

The prevention of left ventricular dysfunction secondary to cancer treatment is still a medical challenge.[2] Drug-induced cardiotoxicity is the main limiting factor for the administration of higher doses of anthracyclines. Addressing the anthracycline-induced cardiotoxicity is particularly important for pediatric cancer survivors, as it remains one of the main causes of morbidity and mortality in this population.[3]

Other classes of antineoplastic agents, such as tyrosine kinase inhibitors, anti-HER2 therapies, and immunotherapy can also have a negative impact on myocardial function.[4] Thus, there is a need for (a) the development of strategies to identify and control cardiotoxicity; (b) further data on the long-term risk in these patients; and (c) effective primary and secondary prevention strategies. It is known that the precise evaluation of baseline characteristics and cardiovascular risk factors allow an individualized approach to each patient.[5]

Cardioprotective therapies represent an important way to reduce the cardiotoxicity secondary to cancer treatment. However, the ideal duration, the strategy and the long-term efficacy of empiric cardio-protection remain unknown.[6] There is still no clear consensus on recommendations for cardioprotective pharmacotherapy. However, it is known that the first step in preventing cardiotoxicity is to be aware of the cardiovascular risk, and to identify the high-risk patients. A pro-active approach is essential, towards the identification of risk factors and pre-existing cardiovascular diseases in oncologic patients.[4,5] This is a continuous process that must be applied during the whole treatment period. In patients who require high doses of anthracyclines, continuous infusion of anthracyclines, the use of liposomal doxorubicin and dexrazoxane have been shown to attenuate cardiotoxicity.[7] Current data do not support the routine use of neuro-humoral antagonists as cardioprotective agents in patients treated with cardiotoxic chemotherapy.[6] This lack of evidence on cardioprotective therapies may be attributed to the high heterogeneity and modest size of the samples in most studies.[6] Although small studies have been included in the meta-analyses, the considerable heterogeneity in the study design and method, as well as in patients' risk makes interpretation and generalization of results quite challenging.[8]

In the absence of definite results from large-scale studies, the question about which patients are most likely to benefit from cardioprotective treatment with neurohormonal antagonists remains unanswered.[6] Although risk-based strategies may be attractive, currently available randomized trials do not support the use of interventions guided by images or biomarkers. This may be explained by the fact that the effect of interventions with neurohormonal antagonists may be lower in the absence of an elevated neurohormonal activation. Besides, in general, neurohormonal antagonists are not specifically targeted to the cardiotoxic effects of anti-cancer treatments, but rather, used to attenuate potential negative effects of neurohormonal activation in response to myocardial lesion. Future studies should develop new targeted cardioprotective agents.[6] In contrast, there is a strong consensus on the importance of a strict control and treatment of risk factors. In this context, the interaction and collaboration among oncologists, cardiologists, and cardio-oncologists play a key role.[9]

The design of larger, collaborative, multicentric studies have been a high priority in cardio-oncology. Fortunately, there is currently an international effort to develop multicentric, randomized trials on cardioprotection.[6] In addition, it is important to incorporate cardiovascular outcomes into pivotal studies in oncology. The design of conventional clinical trials in oncology has been mostly focused on the efficacy of anti-cancer therapy to the detriment of valuable information on cardiovascular risk factors and outcomes. To achieve a balance between efficacy and potential risk of cardiotoxicity of oncologic treatment, research in oncology should integrate baseline cardiovascular data with pre-established cardiovascular outcomes.[6]

The improvement of survival rates in several types of cancer should not be accompanied by an increased risk of treatment-related cardiotoxicity. A continuous search for methods to identify more precisely those patients at higher risk should continue, together with the development of interventions directed at cardio-protection in oncology.

Keywords

Cardiology; Cardiovascular Diseases; Neoplasms; Medical Oncology.

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Review Article

Asymptomatic Ventricular Dysfunction and HFrEF Secondary to Classic Chemotherapy

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Introduction

Advances in oncology, such as better access to the health care system, earlier cancer diagnosis, and new chemotherapies, have led to longer survival of patients with cancer over the last decades.[1] However, this population is vulnerable to drug-related adverse cardiovascular events, like cardiomyopathy, which leads to heart failure and impairs survival and quality of life.[2,3] Among different classes of chemotherapeutic agents, classically anthracyclines and trastuzumab stand out as the most related to cardiomyopathy. Anthracyclines may cause cardiac dysfunction in cancer survivals in 9% of cases depending on risk factors and cumulative dose, and trastuzumab may cause it in 18.6% of cases with adjuvant chemotherapy.[4,5]

Mechanisms of aggression and pathophysiology

Anthracyclines interfere with the replication of rapidly proliferating cancer cells by stabilizing the topoisomerase 2 complex, an enzyme that regulates DNA and RNA synthesis. In cardiomyocytes, as a consequence, they cause double-stranded DNA to break, leading to mitochondrial dysfunction and reactive oxygen species (ROS) release, and subsequent cardiomyocyte injury.[6] Additionally, anthracyclines bind with iron, also leading to ROS production.[7] Anthracyclines cardiotoxicity usually leads to irreversible cardiomyocyte death.

The mechanism of trastuzumab cardiotoxicity is not completely clear, but it is believed that blocking human epidermal growth factor receptor 2 (HER2) leads to growth factor dysregulation, affecting cardiomyocyte growth and homeostasis.[8] However, they rarely lead to cellular death, which partially explains the reversibility of myocardial injury caused by trastuzumab.

Keywords

Cardiotoxicity; Heart Failure; Anthracyclines; Trastuzumab

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Risk factors

There are known risk factors for cardiotoxicity: female sex; age below 18 years or over 65 years; comorbidities, such as hypertension or other previous cardiovascular disease, diabetes, obesity, and renal insufficiency; high cumulative anthracycline dose; chemotherapy association, especially trastuzumab and anthracyclines; genetic alterations, such as trisomy 21 and hemochromatosis; and mediastinal radiotherapy (Table 1).[5,9] The incidence of cardiovascular events in the 10 days after anthracycline administration is less than 2% in the low-risk group and more than 5% in the high-risk group.[10]

Definition of cancer therapy-related cardiac dysfunction

The classic recognized definition of cardiotoxicity is based on changes in left ventricular ejection fraction (LVEF).[12] A 10% drop to a value below 50% or associated with heart failure symptoms during or after the use of a cardiotoxic agent suggests cardiotoxicity.[2] However, the most recent international definition for cancer therapy-related cardiovascular toxicity[13] regarding cardiac dysfunction contemplates not only changes in ejection fraction, but also a global longitudinal strain (GLS) decline and/or a new rise in biomarkers and/or heart failure symptoms (Table 2).

Clinical presentation

Active surveillance regarding cardiac function during chemotherapy with anthracycline and trastuzumab is recommended in current guidelines; thus, patients are commonly still asymptomatic by the time of the diagnosis of cardiotoxicity. Heart failure symptoms are the classic presentation, with signs of congestion. Acute heart failure presentation is possible, requiring hospitalization and even inotropes or mechanical circulatory support.[6]

Subclinical cardiotoxicity markers

Traditionally, LVEF by echocardiogram has been used as a fundamental tool to detect cardiac dysfunction. However, LVEF reduction may represent a late stage of myocardial injury; therefore, it only allows diagnosis at a point where full recovery is less likely. In order to improve detection of cardiotoxicity, there is a growing body of evidence on the use of biomarkers elevation[15] and myocardial strain reduction[16] as subclinical cardiotoxicity markers.

Table 1 – Assessment of cardiotoxicity risk

Therapy-related factors	Patient-related factors
Low risk of cardiotoxicity	
Lower dose ANT (e.g. doxorubicin < 200 mg/m^2, epirubicin < 300 mg/m^2), liposomal formulations	Age > 18 and < 50 years
Trastuzumab without ANT	
Medium risk of cardiotoxicity	
Modest-dose ANT (doxorubicin 200 – 400 mg/m^2 or epirubicin 300 – 600 mg/m^2)	Age 50 – 64 years 1 or 2 CV risk factors, such as hypertension, dyslipidemia, obesity, insulin resistance, smoking
ANT followed by trastuzumab	
VEGF tyrosine kinase inhibitors	
Second- and third-generation Bcr-Abl tyrosine kinase inhibitors	
Proteasome inhibitors	
Combination immune checkpoint inhibitors	
High risk of cardiotoxicity	
Simultaneous ANT and trastuzumab	Age ≥ 65 years > 2 CV risk factors such as hypertension, dyslipidemia, obesity, insulin resistance, smoking Diabetes Underlying CV disease: CAD, PAD, CMP, severe VHD, heart failure
High-dose ANT (doxorubicin ≥ 400 mg/m^2 or epirubicin ≥ 600 mg/m^2)	
Modest-dose ANT plus left chest radiation therapy	
Elevated cardiac troponin post-ANT prior to HER2-targeted therapy	
High-dose radiation therapy to central chest including heart in radiation field ≥ 30 Gy	Reduced or low-normal LVEF (50% – 54%) pre-treatment
VEGF tyrosine kinase inhibitors following previous ANT chemotherapy	Prior cancer therapy

ANT: anthracycline; Bcr-Abl: breakpoint cluster region-Abelson; CAD: coronary artery disease; CMP: cardiomyopathy; CV: cardiovascular; HER2: human epidermal growth factor receptor 2; LVEF: left ventricular ejection fraction; PAD: peripheral artery disease; VEGF: vascular endothelial growth factor; VHD: valvular heart disease. Adapted from Celutkiene et al., 2020.[11]

Table 2 – Cancer therapy-related cardiovascular toxicity

Symptomatic CTRCT (HF)	**Very severe**	HF requiring inotropic support, mechanical circulatory support, or consideration of transplantation
	Severe	HF hospitalization
	Moderate	Need for outpatient intensification of diuretic and HF therapy
	Mild	Mild HF symptoms, no intensification of therapy required
Asymptomatic CTRCT	**Severe**	New LVEF reduction to < 40%
	Moderate	New LVEF reduction by 10 percentage points to an LVEF of 40% – 49% OR New LVEF reduction by < 10 percentage points to an LVEF of 40% – 49% AND either new relative decline in GLS by > 15% from baseline OR new rise in cardiac biomarkers
	Mild	LVEF ≥ 50% AND new relative decline in GLS by > 15% from baseline AND/OR new rise in cardiac biomarkers

CTRCT: cancer therapy-related cardiovascular toxicity; GLS: global longitudinal strain; HF: heart failure; LVEF: left ventricular ejection fraction. Adapted from European Society of Cardiology 2022 Cardio-Oncology Guidelines.[14]

Cardiac troponin I (cTnI) elevation was described in one third of patients after high-dose anthracycline,[16,17] and the degree of cTnI elevation was associated with the cumulative anthracycline dose.[18] This biomarker is also associated with the degree of left ventricular dysfunction. In one cohort, patients reaching cTnI level over 0.5 ng/mL presented significant and persistent LVEF reduction, while patients with transient LVEF decrease had cTnI levels below 0.5 ng/mL.[16-18] In another study, cTnI values persisting > 0.08 ng/mL over a month after therapy was associated with 84% risk of cardiotoxicity, while cTnI below the reference range was associated with 1% risk.[17]

Besides troponins, other biomarkers have been studied in subclinical cardiotoxicity. Natriuretic peptides have controversial correlation with cardiotoxicity in literature. Some evidence suggests an association between NT-proBNP level and cumulative dose of anthracycline.[19,20] However, in two cohorts, while cTn predicted cardiac toxicity, natriuretic peptides did not.[21,22] Markers of

inflammation and endothelial dysfunction are also targets of research,[23] but they are less used in clinical practice.

Early identification of subclinical left ventricular dysfunction is also possible using GLS, which is an evaluation of two-dimensional speckle-tracking that allows for a study of global and regional myocardial deformation to detect subtle alterations in systolic function, particularly related to anthracyclines chemotherapy.[16] The use of GLS could identify patients with higher risk of cardiotoxicity and improve cardiac surveillance.

Evidence from a metanalysis including 21 studies and 1782 patients with cancer suggests that GLS can identify subclinical myocardial dysfunction and that it also has prognostic implications regarding chemotherapy-induced cardiotoxicity or heart failure, despite some limitations of the trials, such as: significant statistical heterogeneity between studies, variable GLS cutoff values, and publication bias.[16] Using this rationale, the SUCCOUR study evaluated a GLS-based approach to initiation of cardioprotection compared to standard care to reduce the risk of future LVEF decrement, interruption of cancer therapy or cancer therapy-related cardiac dysfunction.[24] Anthracycline-exposed patients with another risk factor for heart failure were enrolled to start cardioprotection with an angiotensin-converting enzyme inhibitor and betablocker after 10% LVEF reduction to less than 55% or 5% reduction with symptoms of heart failure or after relative GLS reduction of 12%. Comparing both groups, there was no difference in final ejection fraction. However, at the final follow-up, 44 patients in the GLS-guided arm were treated with cardioprotective drugs versus only 20 patients who received the same treatment in the ejection fraction-guided arm. As a result, 21 patients (13.7%) in the ejection fraction-guided arm, compared to only 9 patients (5.8%) in the GLS-guided arm, met criteria for cancer therapy-related cardiac dysfunction ($p = 0.022$). In a post-hoc analysis, the study also showed lower reduction in the ejection fraction among GLS-treated patients (2.9%) compared to ejection fraction-treated patients (9.1%).[24]

Monitoring

The frequency of cardiovascular evaluation in monitorization of cardiotoxicity depends on both cardiovascular risk, which involves individual risk factors, and intrinsic chemotherapy risk, leading to different protocols based on individual risk.

The European Society of Cardiology published in 2022 the Cardio-oncology Guidelines,[14] in which they suggest monitorization using echocardiogram (including GLS and 3D LVEF), electrocardiogram, and biomarkers in order to identify subclinical markers of cardiotoxicity and consider cardioprotective medications based on individual cardiovascular risk and type of chemotherapy.

The Brazilian Cardio-oncology Guideline[14] suggests a slightly different approach (Figures 1 and 2). Different intervals are also used depending on baseline LVEF. For anthracyclines, if baseline LVEF is > 55%, only echocardiogram is recommended after 3, 6, and 12 months. If LVEF is between 50% and 55%, in addition to echocardiogram, troponin and natriuretic peptides analysis is also recommended < 72 hours after exposure to anthracyclines. If LVEF is < 50%, prompt heart failure treatment should be initiated, and first image evaluation should be made after 45 days. For trastuzumab, if LVEF is > 55%, echocardiogram should be done after 12 and 24 weeks and at the end of treatment. If LVEF is between 50% and 55%, besides echocardiogram, troponin and natriuretic peptides analysis is also recommended < 72 hours after exposure. If LVEF is < 50%, prompt heart failure treatment should be initiated, and image evaluation should be made after 12 weeks, 18 weeks, and at the end of treatment.

Primary prevention of chemotherapy-induced cardiomyopathy

Non-pharmacological prevention, such as stopping smoking, consuming healthy diet, and adopting moderate aerobic exercise, should always be stimulated to reduce cardiovascular risk.[25] It is also important to control weight, treat comorbidities, and, if possible, minimize cardiac radiation. Regarding pharmacological therapy, there are two approaches in primary prevention of anthracycline-induced cardiotoxicity: reducing the cardiotoxic effects of anthracycline and initiating cardioprotective medication.

The first approach is possible by decreasing cumulative dose of the agent (< 360 mg/m^2 of doxorubicin or equivalent dose of anthracycline analogues), using continuous infusion and preferring liposomal forms of the drug.[26] Less cardiotoxic anthracycline analogues (epirubicin, idarubicin, and mitoxantrone) should also be preferred.

In the second approach, cardioprotective medications are initiated expecting reduction of myocardial injury. So far, only dexrazoxane has been approved by the United States Food and Drug Administration to avoid anthracycline cardiotoxicity in patients with metastatic breast cancer who have received > 300 mg/m^2 of doxorubicin.[27] Dexrazoxane is an iron chelator that changes topoisomerase 2B configuration, preventing anthracycline interaction and thus preventing its cardiotoxic effect. Different trials have shown reduction of cardiovascular events and of the incidence of heart failure among patients with breast cancer, and a systematic review and meta-analysis of randomized and nonrandomized trials on the efficacy of dexrazoxane in patients with breast cancer showed that dexrazoxane reduced the risk of clinical heart failure (risk ratio: 0.19; 95% confidence interval: 0.09 to 0.40; $p < 0.001$) and cardiac events (risk ratio: 0.36; 95% confidence interval: 0.27 to 0.49; $p < 0.001$), irrespective of previous exposure to anthracyclines, and the rate of partial or complete oncological response, overall survival, and progression-free survival were not affected by dexrazoxane.[7]

Cardiovascular drugs such as beta-blockers, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers have shown controversial results and

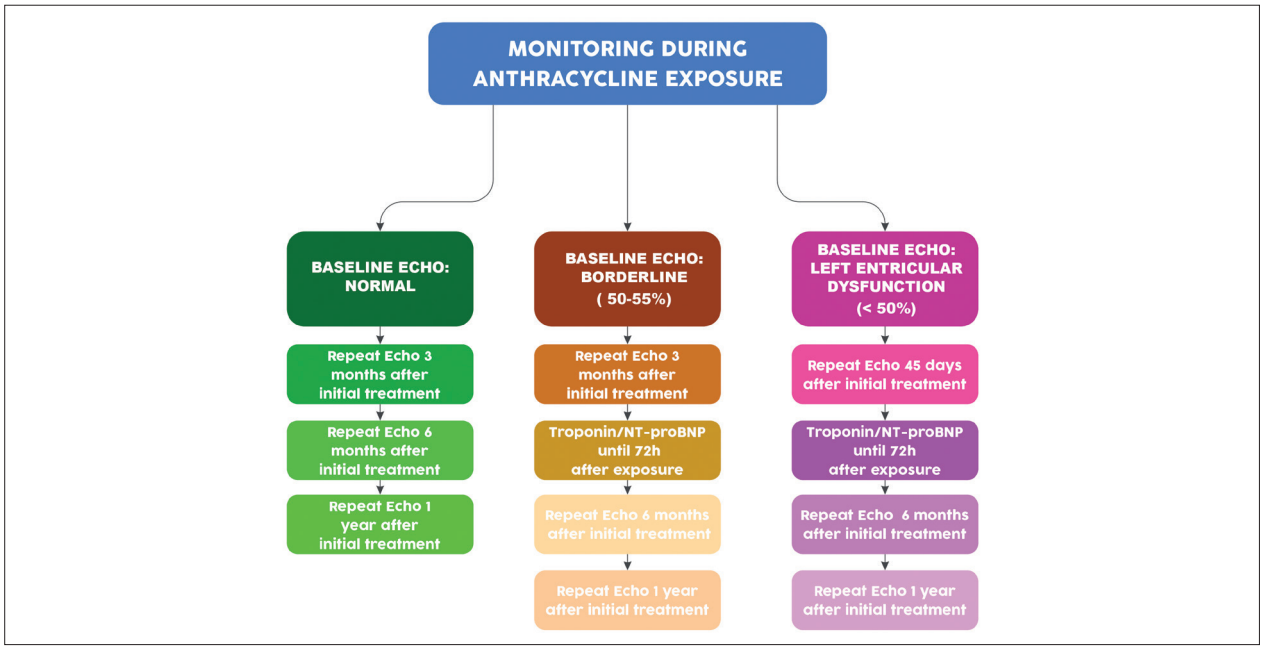

Figure 1 – *Echocardiographic monitoring and analysis of biomarkers in patients using anthracyclines suggested by the Brazilian Society of Cardiology. Echo: echocardiogram; NT-proBNP: N-terminal pro-B-type natriuretic peptide; QT: chemotherapy.*

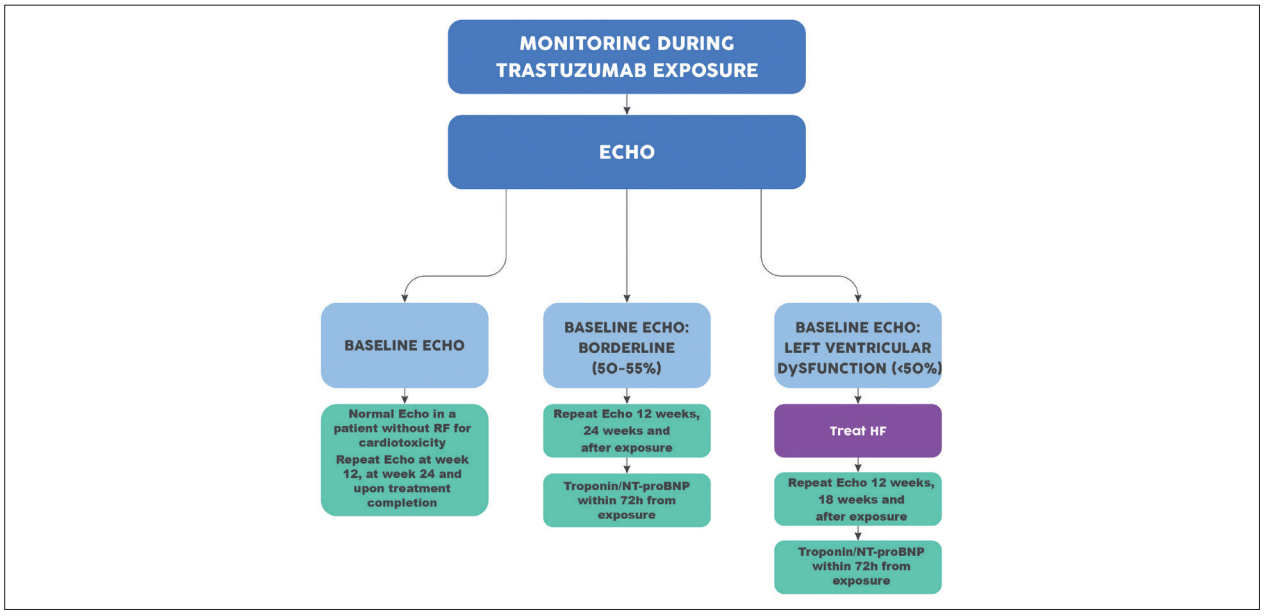

Figure 2 – *Echocardiographic monitoring and analysis of biomarkers in patients using anti-HER2 drugs suggested by the Brazilian Society of Cardiology. Echo: echocardiogram; HF: heart failure; NT-proBNP: N-terminal pro-B-type natriuretic peptide; RF: risk factors.*

are not recommended as a routine in patients under chemotherapy.[24] Earlier small randomized studies suggested that carvedilol[28] and nebivolol[29] were protective against LVEF changes. In one of the first randomized clinical trials comparing placebo versus carvedilol in patients treated with high doses of anthracycline chemotherapy, Kalay et al. found a higher reduction in LVEF in the placebo group (69% to 53%) than in carvedilol (70% to 69%) ($p < 0.001$).[30] Differently, the PRADA (Prevention of cardiac dysfunction during adjuvant breast cancer therapy)[31] trial evaluated cardioprotection using metoprolol and candesartan in 130 patients and showed benefit of candesartan with a less pronounced decrease in LVEF compared to the metoprolol group and placebo. In 2021, the 2-year result of the PRADA trial[32] also showed that candesartan treatment was associated

with a significant reduction in left ventricular end-diastolic volume compared with the non-candesartan group (p = 0.021) and attenuated decline in GLS (p = 0.046) at 2 years, but no differences were found in the metoprolol group, and there was no difference in cardiac troponins between groups.

Cardinale et al. studied cardioprotection using enalapril, an angiotensin converter inhibitor widely used in the management of heart failure, in 114 patients who developed positive troponin during anthracycline treatment, compared to placebo.[33] The enalapril group had significantly lower incidence of heart failure and asymptomatic ventricular dysfunction. The same author studied 273 patients comparing enalapril in one arm in all patients before chemotherapy versus another arm using enalapril only in patients who developed positive troponin during chemotherapy.[28] There was no difference between groups, suggesting enalapril use could be triggered by troponin elevation. The largest randomized trial evaluating carvedilol versus placebo in cardiotoxicity, the CECCY trial (Carvedilol Effect in Preventing Chemotherapy Induced Cardiotoxicity),[29] included 200 patients with breast cancer and use of anthracyclines, and it showed no difference in LVEF between both groups. There was a slight decrease in left ventricle diastolic diameter in the carvedilol group. However, the rate of events was lower than calculated (14.5% in the carvedilol group and 13.5% in the placebo group), which may have interfered with the results. Interestingly, despite the negative primary outcome, the carvedilol arm had lower troponin values than the placebo arm, raising the possibility of subclinical cardiotoxicity protection. Table 3 shows the main trials evaluating cardioprotective medications in primary prevention.

Treatment of asymptomatic and symptomatic ventricular dysfunction

During cancer treatment, if LVEF drops below 50%, cardioprotective medications should be promptly started.[14,24] Depending on the severity of cardiac dysfunction, chemotherapy should be interrupted, but discontinuation should be always discussed in a multidisciplinary team. In general, guidelines recommend that when LVEF drops below 40%, antineoplastic treatment should be suspended temporarily. The feasibility of returning the same chemotherapy depends on the involved agent and multidisciplinary team discussion (Figures 3 and 4).

GLS reduction and a rise in biomarkers[39] are now incorporated in both Brazilian and European guidelines as markers of subclinical injury, and both guidelines

Table 3 – Summary of the most important clinical trials in primary prevention of cardiotoxicity

Study	Patients	Chemotherapy Regimen	Cardioprotective Drug	Primary Outcome	Follow-up (months)
Cardinale[33] 2006	114	Epirubicin Idarubicin Daunorubicin	Enalapril	Cardiotoxicity incidence: Control: 43% Enalapril: 0% p < 0.001	12
Kalay[30] 2006	50	Doxorubicin Epirubicin	Carvedilol	LVEF change pre/post chemotherapy Placebo: 68.9%/52.3%; p < 0.001 Carvedilol: 70.5%/69.7%; p = 0.3	6
Georgakopoulos[34] 2010	125	Doxorubicin	Metoprolol Enalapril	No change in LVEF	12
Bosch[35] 2013/ OVERCOME	201	Idarubicin Daunorubicin	Carvedilol Enalapril	Mean change in LVEF reduction (%) Control: −3.1; p = 0.035 Enalapril + Carvedilol: −0.17%; p = ns	6
Kaya[36] 2013	45	Doxorubicin Epirubicin	Nebivolol	LVEF change pre/post chemotherapy Placebo: 66.6%/57.5%; p = 0.001 Nebivolol: 65.6%/63.8%; p = 0.5	6
Gulati[28] 2016/PRADA	126	Epirubicin	Metoprolol Candesartana	Mean change in LVEF reduction (%) Placebo: −2.6 Candesartan: 0.8; p = 0.026 Metoprolol: −1.6%; p = ns	6
Pituskin[37] 2017/MANTICORE	94	Trastuzumab	Bisoprolol Perindopril	No change in LVEF	12
Avila[29] 2018/CECCY	200	Doxorubicin	Carvedilol	No change in LVEF	6
Guglin[38] 2019	468	Trastuzumab	Lisinopril Carvedilol	Cardiotoxicity rate Placebo 47% versus lisinopril 37% versus carvedilol 31%	12

ACEI: angiotensin-converting enzyme inhibitor; LVEF: left ventricular ejection fraction; ns: not significant.

recommend considering cardioprotective medications in this scenario.

Prognosis

Despite contemporary heart failure treatment, up to 36% of patients with anthracycline-induced cardiotoxicity do not experience complete recovery when treatment is started within 2 months after the end of chemotherapy, and this percentage gradually decreases after this time.[40,41] In order to avoid decreasing LVEF and exposing patients to the risk of irreversible cardiac dysfunction, even with heart failure treatment, prevention of chemotherapy-induced cardiotoxicity has been the focus of research in the last years.

Conclusion

The increasing number of cancer survival patients is also leading to an increasing number of patients suffering from chemotherapy complications, especially cardiotoxicity. Since most patients using anthracyclines do not recover cardiac function completely, the prevention of cancer therapy-related cardiac dysfunction is fundamental, especially by controlling cardiovascular risk factors and encouraging physical activities. Current evidence suggests that it is possible to identify patients with subclinical myocardial damage and, therefore, identify the subgroup that could benefit from intensive surveillance and cardioprotective medications, in order to reduce morbimortality in this population.

Author Contributions

Conception and design of the research, Acquisition of data and Critical revision of the manuscript for important intellectual content: Avila MS, Belfort DSP, Martins SM, Hajjar LA; Analysis and interpretation of the data and Writing of the manuscript: Avila MS, Belfort DSP.

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Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

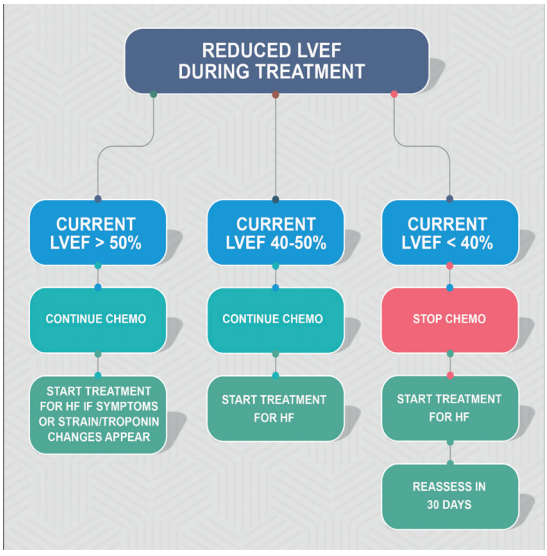

Figure 3 – *Algorithm of the Brazilian Society of Cardiology for the management of heart failure and ventricular dysfunction induced by anthracyclines. chemo: chemotherapy; HF: heart failure; LVEF: left ventricular ejection fraction.*

Figure 4 – *Algorithm of the Brazilian Society of Cardiology for the management of heart failure and ventricular dysfunction induced by anti-HER2 therapy. chemo: chemotherapy; HF: heart failure; LVEF: left ventricular ejection fraction.*

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Review Article

Heart Failure with Preserved Ejection Fraction and Cancer

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Abstract

Heart failure with preserved ejection fraction (HFpEF) is associated with high morbidity and mortality. After hospitalization for heart failure, the 5-year survival of HFpEF is 35%, which is worse than many forms of cancer. HFpEF and cancer share common risk factors. The use of chemotherapy medications such as anthracyclines is associated with increased aortic stiffness and diastolic dysfunction, suggesting that anthracycline therapy may increase the risk of HFpEF, given that worsening of diastolic function, which can be associated with the occurrence of HFpEF, is an early sign of cardiotoxicity. Radiotherapy, widely used in the treatment of breast cancer, leads to an increased risk of developing heart disease since radiation induces coronary microvascular endothelial damage and inflammation, leading to microvascular rarefaction, myocardial inflammation, oxidative stress, and fibrosis, which favor the development of HFpEF. Early diagnosis of cardiotoxicity is an important issue in the care of patients with cancer, and biomarkers have been extensively studied in predicting systolic dysfunction and heart failure with reduced ejection fraction, as well as in the development of HFpEF. HFpEF and cancer have an elevated prevalence, and they share age group, risk factors, and the pathophysiological phenomenon, in which inflammation plays a preponderant role. Biomarkers, especially natriuretic peptides, and ultrasound imaging are fundamental tools in the diagnostic detection and follow-up of these patients.

Introduction

Most elderly patients who develop heart failure (HF) have heart failure with preserved left ventricular ejection fraction (HFpEF). Patients with HFpEF have severe symptoms of exercise intolerance, poor quality of life, frequent hospitalizations, and increased mortality.[1] HFpEF is associated with high morbidity and mortality. After hospitalization for HF, the 5-year survival of HFpEF is 35%, which is worse than many forms of cancer.[2]

Keywords

Heart Failure with Preserved Ejection Fraction; Cancer; Cardiotoxicity; Chemotherapy; Radiotherapy

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Cancer became the second leading cause of death in Brazil in 2006, and it is expected to surpass cardiovascular diseases (CVD) in 2025.[3] The progressive increase in the incidence of cancer in developed countries has been attributed to population growth and aging, sedentary lifestyle, and dietary pattern. HFpEF and cancer share common risk factors (Figure 1),[4] such as obesity, sedentary lifestyle, hypertension, smoking, diabetes mellitus, older age group, and dietary pattern. Cancer treatment with chemotherapy has increased survival, but it has also increased the risk of cardiotoxicity, the incidence of ventricular systolic dysfunction, and even irreversible cardiomyopathy, which can range from 3% to 26%.[5]

In cardio-oncology, research and clinical monitoring of cardiotoxicity have mainly focused on asymptomatic reductions in left ventricular ejection fraction (LVEF), which we call cancer therapy-related cardiac dysfunction, or heart failure with reduced ejection fraction (HFrEF). However, it is increasingly recognized that different cancer therapies can have adverse cardiovascular (myocardial, vascular, and metabolic) effects that predispose patients to develop HFpEF. Moreover, many patients with cancer may be at a risk of HFpEF due to the presence of different cardiovascular risk factors related to the presence of comorbidities or cancer-related cardiometabolic effects. HFpEF has not been among frequently collected data in clinical trials involving patients with cancer; therefore, the exact incidence and relative risk compared to controls of patients without cancer, as well as between different cancer treatments, remain unknown. Although future research is needed to understand the incidence of HFpEF in cancer survivors, healthcare professionals should now be aware that many cancer therapies can increase the risk of both HFrEF and HFpEF.[6]

Classification

De Boer et al.[7] proposed a 5-tier classification system to better characterize the intersection between cardiology and oncology (Figure 2). Types I and II of the classification system address how cancer and cancer therapies affect the cardiovascular system, while types III and IV address how CVD, monitoring strategies, and therapies can contribute to unmasking cancer or promote a favorable environment for tumor development. Type V addresses systemic and genetic conditions that can lead to both CVD and cancer.

Cardio-oncology syndrome type I – Effect of the presence of cancer on the cardiovascular system

Patients with cancer are at greater risk of developing venous and arterial thromboembolic events, and the risk of arterial thromboembolism varies according to the type of cancer. [8] Particularly lung, gastric, and pancreatic cancer have been shown to have higher risks.[7]

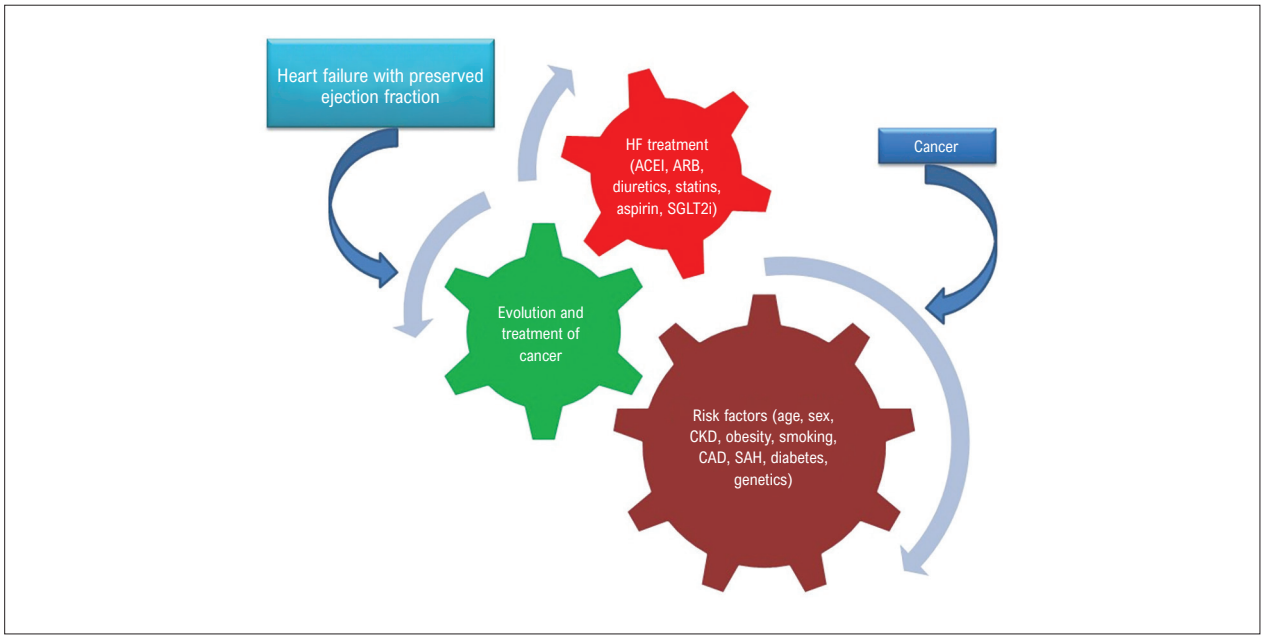

Figure 1 – *Interaction between heart failure and cancer involving risk factors, heart failure treatment, and cancer treatment. Adapted from Wouter C. Meijers and Rudolf A. de Boer, reference 4. ARB: angiotensin receptor blocker; ACEI: angiotensin-converting enzyme inhibitor; CAD: coronary artery disease; CKD: chronic kidney disease; HF: heart failure; SAH: systemic arterial hypertension; SGLT2i: sodium-glucose cotransporter-2 inhibitor.*

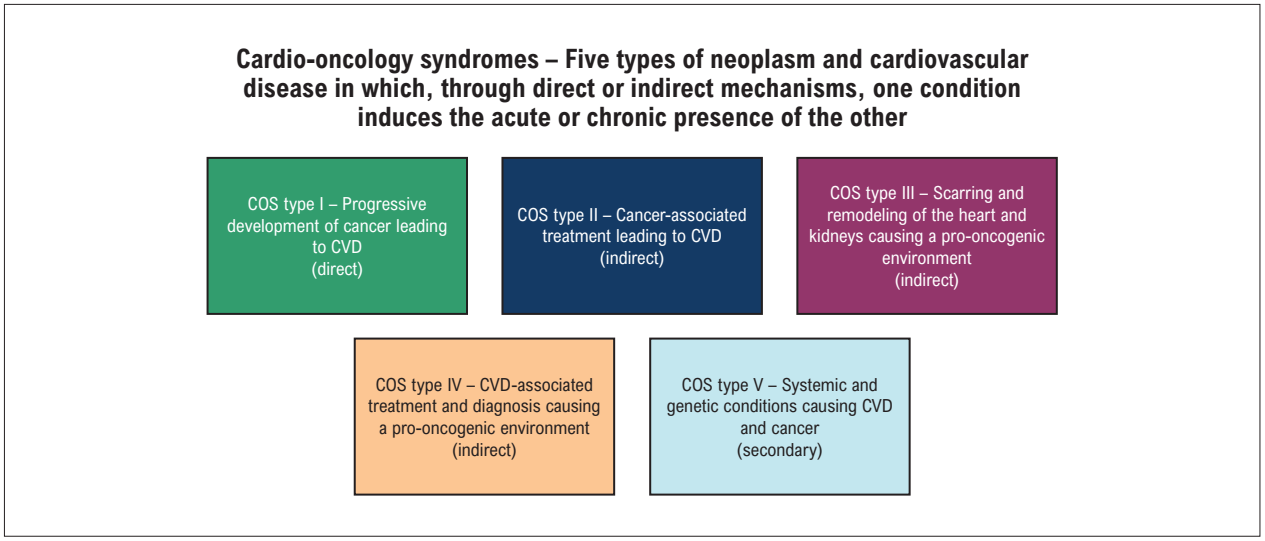

Figure 2 – *Cardio-oncological syndromes: The five types of cardio-oncological syndromes are classified as direct, indirect, or secondary. Adapted from de Boer RA reference 7. CVD: cardiovascular disease; COS: cardio-oncological syndrome.*

Cachexia is a state of involuntary weight loss. It is commonly seen in patients with cancer, and it has an impact on the heart. Cancer-associated cachexia is characterized by the secretion of inflammatory mediators and hormonal factors from tumors and their microenvironment. Eating disorders have multiple consequences, such as potentially fatal cardiovascular complications characterized by hemodynamic and structural changes, cardiomyopathy, and premature death.[9]

Cardio-oncology syndrome type II – Cancer treatments cause acute or chronic cardiovascular disease

Modern cancer therapies can lead to structural and functional cardiovascular dysfunction, and cardiotoxicity is one of the most worrying side effects of chemotherapy.[10]

Myocardial dysfunction and HF are important consequences of several classes of commonly used chemotherapy agents, most notably anthracyclines and human epidermal growth

factor receptor 2 antagonists.[11] Although both agents can cause reversible myocardial dysfunction, irreversible myocyte damage is classically reported with anthracyclines and can lead to HF years after drug administration.[7]

Radiotherapy can cause damage to the epicardial arteries and microcirculation both in the short and long term, which can cause regurgitation related to valve retraction and stenosis and induce fibrotic changes in the parietal pericardium.[11]

Cardio-oncology syndrome type III – Cardiovascular disease promotes a pro-oncogenic environment

Epidemiological data suggest an increased risk of cancer in patients with prevalent CVD compared to individuals without CVD. In a Danish study, all age groups demonstrated higher rates of cancer incidence 1 year after the diagnosis of myocardial infarction.[12] The association of CVD with an increased risk of cancer is further supported by a long-term prospective study that evaluated the clinical characteristics and the prevalence of malignancy in patients with acute coronary syndrome during a 17-year follow-up. The incidence rate was 17.8 cases per 1000 person-years in patients with acute coronary syndrome, 3 times higher than that observed in the general population. Patients who developed cancer after the diagnosis of acute coronary syndrome showed worse prognosis.[13]

Atrial fibrillation may also be associated with cancer. The RE-LY Study revealed that malignant tumors were the main cause of non-cardiovascular death in patients with atrial fibrillation.[14,15] Furthermore, the Women's Health Study (WHS) showed that 10% of patients who had new-onset atrial fibrillation developed subsequent cancer.[15] However, most evidence derives from retrospective analyses with primarily non-causal relationships. Furthermore, available data tend to show positive associations, due to publication bias.[7]

Cardio-oncology syndrome type IV – Association between CVD treatments and diagnostic methods and cancer

Studies have suggested the possibility of an association of cumulative radiation for cardiovascular diagnosis with subsequent cancer.[16,17] The prevalence of cancer attributed to radiation exposure due to cardiovascular diagnosis has been extensively investigated, and existing data suggest that children and adolescents are more likely to develop radiation-associated malignancies than older individuals.[16,17] Consequently, there has been a discussion about the ideal type of imaging modalities that should be used for specific indications in younger patients with a focus on reducing imaging with exposure to radiation.[7]

Cardio-oncology syndrome type V – Systemic and genetic conditions

Research over the decades has established risk factors, such as smoking, alcoholism, diabetes, obesity, and sedentary lifestyle, associated with the development of cancer and CVD. These factors were previously interpreted as separate entities associated with cancer or CVD. More recently, however, the overlapping model has surfaced in relation to risk factors common to both CVD and cancer.[7,18,19]

While the mechanisms involved in the development of CVD in patients with cancer have largely been elucidated, the pathways that lead to the increased prevalence of malignancies in patients with CVD have not yet been fully explored.[20] There are common molecular pathways central to CVD and cancer, such as inflammation, genetic predisposition, clonal hematopoiesis, that is, inflammation and clonal hematopoiesis of undetermined potential.[7]

Chemotherapy and the risk of HFpEF

The use of anthracyclines can cause left ventricular systolic dysfunction (stage B HF) that can progress to HFrEF. Anthracyclines are associated with increased aortic stiffness[21] and diastolic dysfunction,[22] suggesting that anthracycline therapy may increase the risk of HFpEF, given that the worsening of diastolic function, which can be associated with the occurrence of HFpEF, is an early sign of cardiotoxicity.[23,24]

In several cohort studies, significant changes in echocardiographic measurements of diastolic function have been observed with modern breast cancer therapy, particularly in patients treated with anthracycline therapy.[25,26] Nearly half of patients treated with anthracyclines develop HF. Although the anthracyclines epirubicin and doxorubicin are effective antineoplastic drugs used in the treatment of numerous malignancies, their use is restricted due to serious side effects, the main one being chronic cardiotoxicity followed by HF.[27] The risk of cardiotoxicity is dose-related, and it is promoted by several risk factors.[28] The pathophysiology is complex, but a central mechanism is oxidative stress.[29] Cardiotoxic damage appears in cell membranes, mitochondria, and DNA, affecting both energy metabolism and ion handling.[30,31]

One study showed that the development of diastolic dysfunction was observed in more than 50% of patients treated with anthracycline chemotherapy in the first year of treatment.[25] Using data from SEER-Medicare, breast cancer survivors aged 66 years and older had increased risk of HF compared to controls without cancer.[32] Although the study provided results, use of a statement-based dataset is not able to distinguish between HFpEF and HFrEF, and older women are at a greater risk for both. Further studies are needed to better understand the clinical impact of these changes in vascular and diastolic function; however, we should be aware that cardiotoxicity following anthracycline therapy may present as HFpEF.[6]

Radiotherapy and the risk of HFpEF

Breast-conserving surgery combined with radiotherapy has emerged as the standard approach for treating localized breast cancer, and, in more advanced disease, radiotherapy improves local control and survival.[33,34] The high doses of chest radiation used in treatment of thoracic tumors and older radiotherapy techniques for breast cancer lead to an increased risk of developing heart disease.[35,36] With the advance in radiotherapy planning, including the use of radiotherapy planning assisted by computed tomography, we can achieve a substantial reduction in cardiac radiation exposure during contemporary breast cancer radiotherapy. Nevertheless, even low levels of

cardiac radiation during breast cancer radiotherapy increase the risk of coronary events.[37] Cardiomyocytes are largely resistant to radiation. However, radiation induces coronary microvascular endothelial damage and inflammation leading to microvascular rarefaction, myocardial inflammation, oxidative stress, and fibrosis, which favor the development of HFpEF.[38,39]

The large loss of cardiomyocytes due to myocardial infarction or other factors is the primary etiological insult in HFrEF. On the other hand, the development of microvascular endothelial inflammation due to the presence of comorbidities with similar subsequent myocardial effects may contribute to myocardial dysfunction; it is thus considered a key factor in the pathophysiology of HFpEF.[40] Exposure to cardiac radiation, which functions as a comorbidity, during radiotherapy for the treatment of breast cancer may increase the risk of HF, in particular HFpEF.[40,41]

Studies have documented new cardiac perfusion defects (without transient myocardial infarction) after breast cancer radiotherapy consistent with microvascular rarefaction.[42] Coronary microvascular endothelial inflammation caused by comorbidity is believed to play a key role in the pathophysiology of HFpEF. Microvascular endothelial inflammation leads to microvascular dysfunction and rarefaction with reduced coronary flow reserve and inflammation and to myocardial fibrosis, in addition to oxidative stress, which can impair nitric oxide–cyclic guanosine monophosphate signaling and potentiate cardiomyocyte hypertrophy and diastolic myofibril stiffness.[40]

A study[35] has shown that, in elderly women with breast cancer treated with radiotherapy, the chances of HF after radiotherapy increased with a higher mean dose of cardiac radiation. The predominant form of HF was HFpEF or HF with "intermediate" ejection fraction (40% to 49%), and the odds of any HF and HFpEF increased with mean cardiac radiation dose, even after adjustment for other known risk factors and cancer stage. The mean time since the onset of HF after radiotherapy was 5.8 years. A minority of women developed ischemic events between radiotherapy and the diagnosis of HF, suggesting that myocardial infarction due to epicardial coronary disease was not the predominant mediator of incident HF. The effect of mean cardiac radiation dose on the incidence of HF was still apparent in sensitivity analyses addressing the potential for surveillance bias associated with more advanced cancer stage.[35]

In women over 40 years of age, the lifetime risks of breast cancer (12%) and HF (20%) are significant.[43] Adjuvant radiotherapy reduces breast cancer recurrence and mortality in some subgroups of women; however, the excellent survival after treatment for breast cancer requires attention regarding survival issues, including cardiovascular complications of radiotherapy,[44] and the risk of cardiotoxicity with high-dose thoracic radiotherapy has been well documented.[38,39]

Therefore, in older women undergoing radiotherapy for breast cancer, the relative risk of HFpEF increases proportionally to radiation, begins a few years after radiotherapy, and is not mediated by coronary events alone. These data suggest that radiation dose and risk factors for HF should be considered in decisions about breast cancer radiotherapy, and they underscore the importance of techniques to reduce cardiac radiation dose. Furthermore, there is additional support for the importance of coronary microvascular impairment in the pathophysiology of HFpEF.[35]

The role of inflammation in cancer development in patients with heart failure

Cancer and CVD are currently the main causes of death worldwide, which may suggest that these diseases have pathogenetic mechanisms that are common to both situations. Studies have demonstrated that patients with cancer develop heart disease not only as a consequence of chemotherapy-induced cardiotoxicity, but also because tumor cells release factors that affect various distant organs, including the heart. [45] Cancer-derived pro-inflammatory molecules cause cardiomyocyte atrophy and tissue remodeling, which can degenerate into cachexia and HF.[46]

The causal relationship between HF and cancer has been an important issue of current research, showing controversial results in epidemiological and clinical studies. An elevated risk of cancer incidence has been shown in some studies,[47] reinforcing the hypothesis that HF may predispose to cancer and that a low-grade inflammatory mechanism may mediate both conditions.[46-48]

Extensive evidence has shown that HF is associated with a chronic inflammatory state and activation of the immune response. Inflammation arises locally as a consequence of lesion in HFrEF and systemically as a consequence of various comorbidities in HFpEF.[46]

In HFpEF, inflammation drives the development of HF through a complex sequence of events.[40] Comorbidities induce a systemic pro-inflammatory state. Myocardial disease then begins with coronary endothelial dysfunction and expression of vascular cell adhesion molecules and selectins, which causes leukocyte infiltration. Endothelial cells begin to produce reactive oxygen species which, in turn, trigger a cascade of events with downregulation of nitric oxide production, decreased levels of nitric oxide-stimulated cyclic guanosine monophosphate, and decreased protein kinase G activity.[46]

This sequence of events culminates in protein kinase G-dependent hypophosphorylation of titin, and titin is responsible for cardiomyocyte stiffness, depending on its state of phosphorylation. Stiff cardiomyocytes, in association with interstitial fibrosis and capillary rarefaction, contribute to the loss of diastolic relaxation that is a characteristic of HFpEF.[49] Thus, oxidative stress and inflammation can be considered the consequence or the cause of HF, generating a chronic systemic condition with adverse clinical outcomes. This low-grade, chronic systemic inflammation, however, is often clinically silent, and its consequences can also increase the risk of different types of cancer. According to these observations, genetic polymorphisms in genes encoding anti-inflammatory interleukin (IL)-1β, IL-6, IL-8, and IL-10 have been shown to predispose individuals with HFpEF to cancer.[50]

Several epidemiological and clinical studies have reported that patients with HF are at an increased risk of developing cancer, and chronic low-grade systemic inflammation has been proposed as the main pathophysiological process linking HF and carcinogenesis.[46] There are still unanswered questions that cardiologists and oncologists need to address by means of cooperative actions. The main one is whether HF variants, including most cases of HFpEF, are prone to developing cancer.

Risk factors associated with HFpEF and breast cancer

Advances in cancer treatment have led to increased survival, which is offset by increased risk of long-term comorbidities, including HF.[51] Most studies performed in cardio-oncology have focused predominantly on HFrEF, mainly due to well recognized associations between cancer treatment and reduced LVEF.[52,53] The development of HFpEF in breast cancer survivors is an understudied topic, even though HFpEF is more common than HFrEF in older women, and breast cancer and HFpEF share multiple risk factors, for example, obesity and hypertension.[54]

It is currently unclear to what extent differences in risk factors for HF subtypes hold true for breast cancer survivors for whom cancer treatment may alter the causal pathways of traditional risk factors.[35] For example, elevated body mass index and increased central adiposity are associated with a decline in LVEF in cancer survivors,[55] even though there is no relationship between obesity and LVEF in the general population.[56] There are few data on the incidence of HFpEF and the risk factors associated with HFpEF in breast cancer survivors.[53]

A study[53] evaluated the incidence of HFpEF and HFrEF in menopausal breast cancer survivors and associations with risk factors. The results demonstrated a relatively higher rate of hospitalizations for HFpEF compared to HFrEF. The study also demonstrated that anthropometric factors, previous history of cardiometabolic disorders, and smoking were associated with an elevated risk of HFpEF; in general, the same characteristics were suggestive of an elevated risk of HFrEF, indicating that breast cancer survivors are affected by conventional risk factors for HF subtypes.[53]

In the literature to date, little attention has been paid to HFpEF in breast cancer survivors,[54] potentially due to the fact that HF diagnosis is largely based on LVEF measurements that can fail to diagnose cases of HFpEF, and associated symptoms of HFpEF, such as lack of air, can be attributed to side effects of chemotherapy/radiotherapy or deconditioning rather than HFpEF. In most clinical trials on breast cancer and cardioprotection, the focus of monitoring during treatment has been based on LVEF, rather than a more holistic view of cardiac function that incorporates diastolic parameters in addition to systolic function.[57]

In the same manner that has been observed in population studies,[54] the study observed a higher incidence of HFpEF in this elderly population of breast cancer survivors. Despite an increased risk of HFpEF in older women, the HFpEF phenotype remains an understudied component after breast cancer. However, HFpEF contributes to an equal proportion of hospitalizations as HFrEF and an equally increased risk of long-term mortality after diagnosis.[58] Risk factors for HF were very similar to that of the general population, with the exception of prior myocardial infarction for HFpEF. Notably, both waist circumference and smoking represent potentially modifiable factors.[53]

Biomarkers in the prediction and diagnosis of HFpEF in patients with cancer

Therapies used to treat cancer, particularly anthracyclines and trastuzumab, can damage the heart. Most studies have focused on asymptomatic left ventricular dysfunction caused by these agents and HFrEF. However, although little recognized, these treatments can cause cardiac, vascular, and metabolic damage that can evolve with HFpEF. This can occur as an initial manifestation and later evolve to HFrEF or even be the only manifestation, during treatment or months after treatment, in cancer survivors.[59] Furthermore, due to the presence of comorbidities and the direct effect of the cancer itself, these patients have an increased baseline risk of developing HFpEF (Figure 3).[59]

Biomarkers are substances secreted into the circulation or urine that provide us with early information about diagnosis and prognosis in a given condition. In this section, we will address the main biomarkers involved in the prediction of HFpEF and its prognosis, including the classic cardiac biomarkers troponins and natriuretic peptides, as well as systemic, non-cardiac biomarkers related to both cancer and the cardiovascular system. These biomarkers have been extensively studied in the prediction of systolic dysfunction and HFrEF, but they are also related to the development of HFpEF.

Cardiac biomarkers in cancer

Cardiac biomarkers can be used in different ways in the management of cancer patients: 1) before starting cancer treatment, as predictors of cardiac complications during treatment; 2) in monitoring during cancer treatment to detect early cardiotoxicity; and 3) in cancer survivors to monitor long-term cardiotoxicity.

Cardiac troponins

Cardiac troponins T and I are the gold-standard markers of acute myocardial infarction. However, cardiac troponins, especially high-sensitivity cardiac troponins, may be elevated in situations unrelated to forms of myocardial damage other than ischemia, for example, in myocardial injury. They are the main marker used to detect cardiotoxicity in cardio-oncology.[59-61] They can detect early subclinical myocardial alterations, which can guide the prevention of irreversible systolic dysfunction.[60,61] Furthermore, they can predict the risk of cardiotoxicity before beginning cancer treatment. The presence of cardiovascular comorbidities, systemic alterations such as inflammation and oxidative stress, and the effects of cancer itself on the heart can cause elevations in cardiac biomarkers, indicating a greater risk of toxicity.[62] In a study with 452 patients with breast cancer, naive to treatment, the basal dosage of troponins T and I was a predictor of increased risk of developing myocardial dysfunction with trastuzumab treatment.[63] However, there are no specific studies for the prediction of HFpEF.

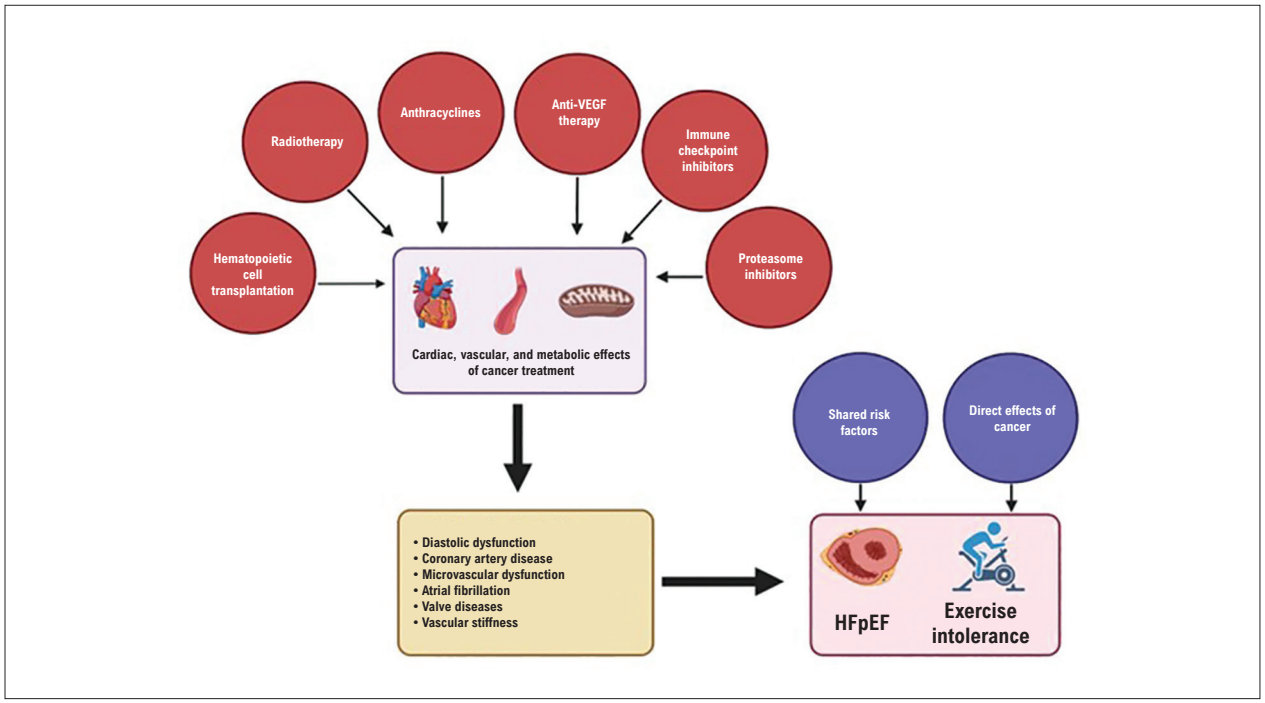

Figure 3 – *Mechanisms involved in the development of HFpEF in patients with cancer. HFpEF can be caused by chemotherapy or radiotherapy leading to diastolic changes, which may be associated with coronary artery disease and atrial fibrillation. Additionally, the patient may have HFpEF even before starting treatment, due to comorbidities common to cancer and HFpEF, as well as due to the direct action of the cancer itself on the myocardium. HFpEF: heart failure with preserved ejection fraction; VEGF: vascular endothelial growth factor.*

Natriuretic peptides

Natriuretic peptides may be increased in patients with cancer undergoing treatment.[60,61,64] In a study of 40 women with cancer (37 with breast cancer, 2 with lymphoma and 1 with sarcoma) treated with doxorubicin, BNP was altered early in the patients who developed left ventricular systolic dysfunction, none of whom developed clinical HF.[64] It is interesting to note that the left ventricular diastolic function parameters on the echocardiogram also changed early, but BNP was the only marker that correlated with the cumulative dose of doxorubicin. Although natriuretic peptide levels may increase with cancer treatment, it has been reported that cancer cells themselves may secrete BNP.[65] Baseline levels of natriuretic peptides, prior to initiation of cancer treatment, are associated with cancer progression and severity. In a study by Pavo et al., with 555 patients with a primary diagnosis of cancer and without previous treatment, NT-ProBNP and other markers (troponins, C-reactive protein, copeptin, IL-6, among others) were elevated according to tumor staging and were predictors of mortality.[66]

Oncological biomarkers and inflammatory markers

Several biomarkers associated with cancer are used as diagnostic and prognostic markers in this disease. Many of them are associated with cardiovascular severity, for example, the New York Heart Association functional class, and cardiovascular mortality outcomes.[60] They also correlate with natriuretic peptide levels. Among oncological markers and inflammatory markers, we can mention CA125, CEA, galectin-3, GDF-15, PlGF, CHIP, IL-1, IL-6, IL-8, C-reactive protein, TNF-a, ST2, and myeloperoxidase.[60]

Figure 4 displays the bidirectional relationship between cancer and the heart, with cardiac biomarkers predicting cardiac complications from cancer, and inflammatory and cancer-related biomarkers predicting cancer itself and cardiac complications.

Perspectives for biomarkers in HFpEF

Most studies to date have evaluated the role of biomarkers in predicting left ventricular systolic dysfunction or mortality outcomes. There are no specific studies on the prediction of HFpEF. However, ongoing studies may eventually identify useful markers in this bidirectional relationship between CVD and cancer, including baseline HFpEF or HFpEF acquired after cancer treatment.

A recent study identified the biomarker of collagen type XXVIII that may play a role in the future. Collagen XXVIII was recently described; it is located at the interface between the basement membrane and the interstitial matrix, and it may be involved in tissue repair.[67] Reese-Petersen et al. developed an ELISA technique that is able to detect the C-terminal fragment of type XXVIII collagen, known as PRO-C28. They observed that this biomarker is elevated in HFpEF and in patients with various types of cancer compared to healthy individuals.[67] This elevation was more significant in lung cancer, where the area under

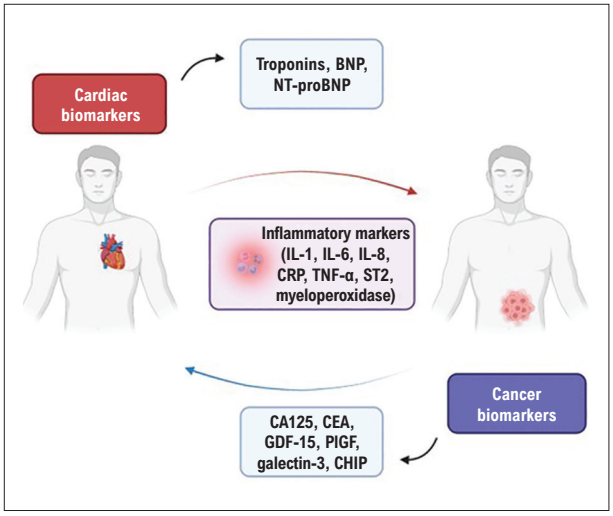

Figure 4 – *Bidirectional relationship between the heart and cancer. Cardiac biomarkers assess the impact of cancer and cancer treatments on the heart, and cancer and inflammatory biomarkers are also predictors of cardiovascular severity in cancer. BNP: brain-type natriuretic peptide; CA125: carbohydrate antigen 125; CEA: carcinoembryonic antigen; CHIP: clonal hematopoiesis of undetermined potential; CRP: C-reactive protein; GDF-15: growth differentiation factor-15; IL: interleukin; NT-proBNP: N-terminal prohormone of brain natriuretic peptide; PIGF: placental growth factor; ST2: suppression of tumorigenicity 2; TNF-α, tumor necrosis factor alpha.*

the curve was 98% for differentiating individuals with lung cancer from healthy individuals. Furthermore, PRO-C28 correlated with NT-proBNP levels. Future studies should establish the usefulness of this new marker in predicting HFpEF in patients with cancer, as well as its prognostic role.

Role of biomarkers in the diagnosis of HFpEF in patients with cancer

The diagnosis of HFpEF in patients with cancer is made in the same way as in patients without cancer, although there is no validation in specific studies in this population. In general, HFpEF is characterized in patients with signs and symptoms of HF, cardiac structural alterations in the presence of LVEF ≥ 50%, and natriuretic peptide elevation.[68] Two risk scores can be used in the diagnosis of HFpEF, the H2FPEF score and HFA-PEFF score (of the European Society of Cardiology). The HFA-PEFF score uses natriuretic peptides in its flowchart.[68] The detailed steps for the diagnosis of HFpEF are beyond the scope of this review, but they can be found in the Brazilian Heart Failure Guideline.[68]

Immune checkpoint inhibitors and HFpEF

Immune checkpoint inhibitors (ICIs) represent an innovative treatment for a large number of cancer types. ICIs have been prescribed for primary tumors and metastases, as well as adjuvant and neoadjuvant therapy. ICIs become toxic because they lead to autoimmune processes that affect all organs. Regarding the heart, it has been noted that ICIs lead to acute HF with preserved or reduced LVEF and even to death by several mechanisms, such as myocarditis, pericarditis, arrhythmia, and takotsubo cardiomyopathy.[69]

Therefore, there is a need for improved methods for detection and risk stratification of heart diseases associated with the use of ICIs, including myocarditis. The study by Mahmood et al.[70] in patients using ICIs showed that, among patients who developed myocarditis, ECG was altered in 89%; NT-ProBNP was elevated in 66%, and only 49% of patients had LVEF below 50%.[70]

The study showed that, among patients with myocarditis due to the use of ICIs, global longitudinal strain, which is a sensitive marker of cardiotoxicity among patients receiving standard chemotherapy, was lower among patients with preserved and reduced LVEF. In the follow-up of these patients, decreased global longitudinal strain was strongly associated with major adverse cardiac events in myocarditis due to ICI use and, more importantly, among those with preserved LVEF.[70] Thus, to identify myocardial involvement and establish the risk of HFpEF, global longitudinal strain is useful in monitoring patients with cancer receiving ICI therapy.

Imaging in HFpEF associated with cancer

The detection of HFpEF associated with cancer is related to cardio-oncological syndromes types I, II and V according to de Boer RA et al.[7] (Figure 2), as previously mentioned in this article. For imaging diagnosis of this HF phenotype, comprehensive transthoracic echocardiogram is the most widely used tool, providing information on 3 basic phenomena that must be detected:

1 – Presence of normal or very slightly reduced global systolic function;

2 – Atrioventricular remodeling, including left atrial and right chamber dilation, but not including left ventricular dilation;

3 – Diastolic dysfunction causing pulmonary circulation overload.

In this context, according to the most recent European Society of Cardiology Guideline on Cardio-oncology,[71] the respective suggested ultrasound indices are as follows:

1 – LVEF, estimated by the 3- or 2-dimensional method

2 – Dimensions, chamber volumes, and cardiac mass indexed by body surface area;

3 – E and A velocities of diastolic inflow in the left ventricle, e' and a' diastolic velocities of the myocardium, the E/e' ratio of estimated diastolic pressure in the left ventricle, the rate of myocardial deformation (global longitudinal strain), and estimated pulmonary pressure, translating the repercussion of left chamber pressures on pulmonary circulation (Figure 5).

Other parameters related to right ventricular function, heart valves, and the pericardium have also been also suggested for pre-therapy baseline examination of the specific neoplasm and follow-up.

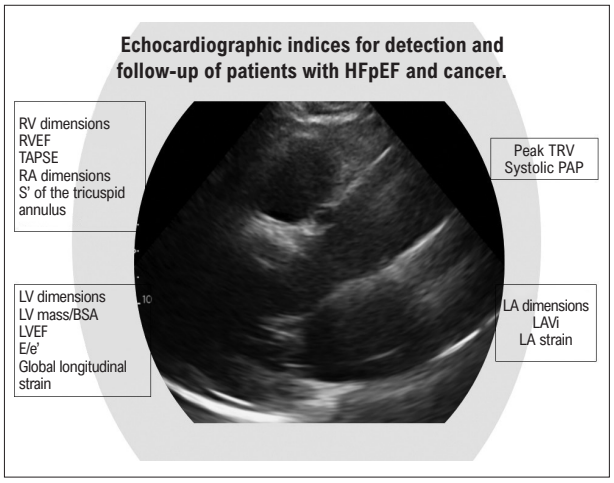

Figure 5 – *Echocardiographic indices for detection and follow-up of patients with HFpEF and cancer. BSA: body surface area; E/e': ratio of early diastolic mitral inflow velocity to early diastolic velocity of the mitral annulus; HFpEF: heart failure with preserved ejection fraction; LA: left atrium; LAVi: left atrial volume indexed by body surface area; LV: left ventricle; LVEF: left ventricular ejection fraction; PAP: pulmonary artery pressure; RA: right atrium; RV: right ventricle; RVEF: right ventricular ejection fraction; S': systolic velocity obtained by Doppler tissue imaging; TAPSE: tricuspid annular plane systolic excursion; TVR: tricuspid regurgitation velocity.*

In the pre-cancer therapy evaluation, the indices of LVEF[72] and global longitudinal strain are used as the main baseline markers, as well as for monitoring cardiotoxicity during chemotherapy. Especially in patients who already present diagnosis of HFpEF, global longitudinal strain is a more sensitive summary marker than ejection fraction. In patients from a case series of 2234 patients in pre-therapy with anthracyclines, global longitudinal strain and left ventricular end-diastolic volume indexed to body surface area volume (LVEDVI) stood out as independent predictors of major cardiac events. When compared, the means for global longitudinal strain of patients who presented the event were lower (−17.8% ± 2.5% versus −16% ± 2.5%; p = 0.0015), and the means for LVEDVI were higher in patients who developed events (53 ± 12 ml/m^3 versus 61 ± 5 ml/m^3; p = 0.02). It is noteworthy that, in this study, LVEF was not statistically significant as a risk predictor in this type of population with preserved systolic function (54% ± 3% versus 53% 3%; p = 0.27).[73] Therefore, from the point of view of risk prevention, determination of initial global longitudinal strain using the speckle tracking technique is well supported and recommended, especially in patients at moderate or high risk of developing toxicity.[74]

Diastolic dysfunction on pre-cancer treatment examination may be associated with an increased risk of systolic dysfunction. Upshaw et al. detected, in a population of participants undergoing treatment for breast cancer, that diastolic dysfunction was associated with a subsequent decrease in LVEF (2.1%; 95% confidence interval: 3.1 to 1.2; p < 0.001) and worsening in longitudinal strain (0.6%; 95% confidence interval: 0.1 to 1.1; p = 0.013) over time. Changes in E/e' were not statistically significant.[22]

From a contemporary point of view, the most recent consensus on cardio-oncology published this year lists the following as class I recommendations: a) echocardiography as a first-line modality for assessing function in cancer patients; b) 3-dimensional echocardiogram as the preferred echocardiographic modality for measurements; c) global longitudinal strain, if available, in all patients with cancer; d) comprehensive echocardiography in all patients with cancer and high risk or very high risk of cardiovascular toxicity before initiating cancer treatment.

Other imaging tests may also be useful in HFpEF and cancer. Chest computed tomography or cardiac magnetic resonance imaging can elucidate images of patients with difficult acoustic windows and identify subclinical ischemic disease and intracardiac masses. Functional exams that provoke ischemia are also important in patients with HFpEF and elevated pre-test probability of significant atherosclerotic disease, especially in patients in need of treatment with drugs with vascular toxicity, such as fluoropyrimidines, vascular endothelial growth factor inhibitors, tyrosine-kinase inhibitors, among others.[75]

Conclusion

HFpEF and cancer have an elevated prevalence, with a growing trend. They share age group, risk factors, and the pathophysiological phenomenon, in which inflammation plays a preponderant role. Biomarkers, especially natriuretic peptides, and ultrasound imaging are fundamental tools in diagnostic detection and follow-up. It is important to emphasize that we are following a huge evolution in treatments, both for HFpEF and for neoplastic diseases, but, in this review, we have found many gaps in knowledge involving populations where both clinical conditions overlap.

Author Contributions

Conception and design of the research; Acquisition of data; Writing of the manuscript; Critical revision of the manuscript for important intellectual content: Jorge AJL, Villacorta H, Danzmann LC, Mesquita ET.

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Study association

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Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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Review Article

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

Myocarditis; Neoplasms; Cardiotoxicity; Immune Checkpoint Inhibitors; Drug Therapy; Immunotherapy

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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 registry[13] 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 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]

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]

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-κB), 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 thymoma[26] 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-β1). TGF-β1 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.

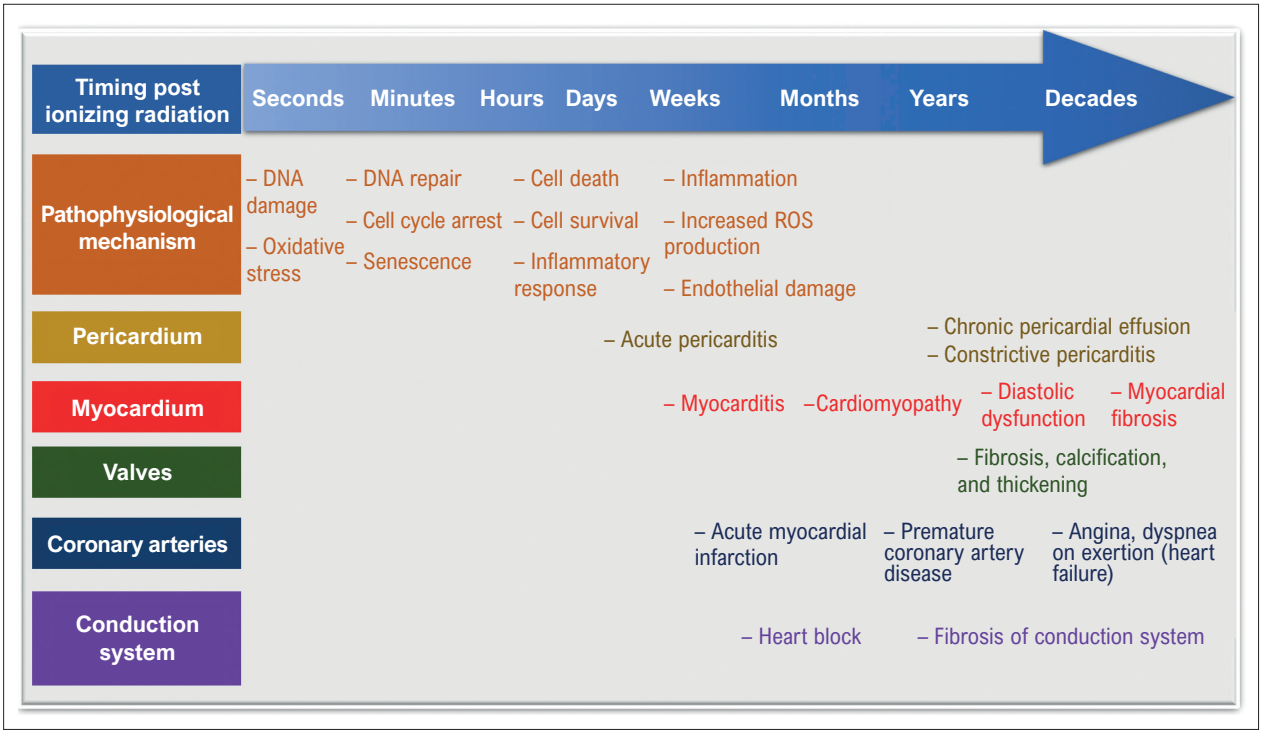

Figure 1 – *Sequence of cardiovascular changes after exposure to ionizing radiation. Source: Adapted from Liu et al., 2022.[38]*

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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Review Article

Pericardial Disease in Patients with Cancer

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Abstract

Pericardial effusion can develop in patients with acute pericarditis or in association with a wide variety of systemic diseases and is characterized as transudative, exudative, pyopericardium, or hemopericardium. Large effusions are usually related to tuberculous or neoplastic effusions. Primary pericardial tumors are rare, with the vast majority of cases resulting from secondary tumors. Pericardial effusion may be present in 7% to 53% of patients with cancer and is correlated with an advanced stage of the disease. The main types of cancer related to pericardial involvement are lung, breast, blood, and gastrointestinal cancers. The clinical presentation is variable; some patients are asymptomatic, whereas up to one-third may develop cardiac tamponade. In general, the severity of pericardial effusion ranges from moderate to significant, and the diagnostic process should focus mainly on the search for the primary disease and on the hemodynamic condition. The presence of pericardial effusion portends a grave prognosis, and treatment depends on the malignancy. Interventional treatments in patients with cancer include pericardiocentesis, pericardial window, and surgical pericardiectomy.

Introduction

The pericardial space consists of a potential cavity between the visceral and parietal peritoneum, which contains approximately 15 mL to 50 mL of plasma ultrafiltrate. The pathological accumulation of fluid in the pericardial space is called pericardial effusion (PE). PE is a common disease with a broad clinical spectrum, ranging from small asymptomatic effusions to cardiac tamponade.[1,2] The main pericardial syndromes are acute or chronic pericarditis, PE, and constrictive pericarditis.

PE etiology basically depends on the clinical presentation of the patient. The main causes include infections (viral, tuberculosis), cancer (lung, breast, lymphoma), rheumatic diseases (lupus, rheumatoid arthritis), metabolic diseases (uremia, hypothyroidism), aortic dissection, and postcardiac injury syndromes (postinfarction, postpericardiotomy).[3] In addition, the increasing number of invasive procedures has led to an increase in the rates of iatrogenic strokes, which result from myocardial perforation during pacemaker implantation, radiofrequency ablation, or cardiac catheterization.[4]

Keywords

Etiology Pericardial Effusion

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Etiology Pericardial Effusion

Corey et al.[5] evaluated 57 patients with PE > 10 mm and reported that the most frequent etiology was infectious (27%), followed by neoplastic (23%). In a study of 322 patients with PE > 10 mm,[6] the most frequent etiology was idiopathic (29%), followed by iatrogenic (16%) and neoplastic (13%); 37% of participants developed cardiac tamponade. A study by Levy et al.[7] evaluated 204 patients with PE, and the most frequent etiologies were idiopathic (48%), infectious (16%), and neoplastic (15%). In our study of 254 patients with PE, the most common etiology was idiopathic (33.1%), followed by postsurgical (19.3%), neoplastic (16.9%), and postprocedural (8.7%).[4]

The clinical context in which PE occurs provides important diagnostic clues, such as the presence of cancer, collagenosis, tuberculosis, myocardial infarction, acute pericarditis, hypothyroidism, or renal failure.[7]

In patients with small PEs and no hemodynamic repercussions, inflammatory signs, or suspected potentially treatable systemic diseases, etiological investigation is usually unnecessary. In these cases, clinical evaluation and serial echocardiography are sufficient.[2]

Epidemiology

Primary pericardial tumors are rare, with the vast majority of cases resulting from secondary tumors. PE may be present in 7% to 53% of patients with cancer and is correlated with an advanced stage of the disease.[8,9] Related mechanisms are implantation of tumor cells in the pericardium by direct extension, hematogenous or lymphatic dissemination of the primary tumor, chemotherapy- or radiotherapy-induced toxicity, and opportunistic infection related to cytotoxic immunosuppression and rapid immune response.[10-12]

In most cases, PE is secondary to a primary tumor. Cancers more typically associated with pericardial involvement are lung, breast, blood (mostly lymphoma and leukemia), and gastrointestinal cancers.[13] Similarly, cardiac tamponade could be present in 32% of cases, with a recurrence rate of 10%.[14]

In our series, the most frequent type was lung cancer, followed by lymphoma and breast cancer.[15]

PE in patients with cancer has prognostic value. According to the results of the study by Wagner et al.,[16] carried out in a tertiary care center for patients with cancer, 11% of those with PE undergoing surgical drainage had hemodynamic instability (pressor-dependent hypotension requiring intensive care unit admission), which portends a grave prognosis with a median survival of 35 days after the procedure.

Clinical presentation

The clinical presentation of PE is variable, ranging from asymptomatic patients to patients with nonspecific complaints and those with systemic symptoms typical of the underlying cancer, such as weight loss, asthenia, cough, palpitations, hemoptysis, malaise, weakness, fatigue, and nausea and vomiting. Up to one-third of patients may develop cardiac tamponade with clinical presentation of jugular distention, muffled heart sounds, hypotension, and paradoxical pulse (a drop in systolic blood pressure of 10 mm Hg during inspiration). Other possible symptoms are tachycardia, pericardial friction rub, arrhythmia, ascites, and peripheral edema.[12,17]

Diagnostic tests

Electrocardiogram

Although electrocardiographic findings are usually normal, the most frequent changes found in patients with cancer and PE are sinus tachycardia and low QRS voltage in the presence of cardiac tamponade (61% of cases), which is defined as amplitude < 0.5 mV in limb leads. Occasionally, new-onset atrial fibrillation and electrical alternans may also be found.[10,17]

Chest radiography

Although chest radiography is not highly specific, it may show an enlarged heart, which is suggestive of significant PE. It may also show other findings, such as pleural effusion and abnormalities in the lung parenchyma.[18]

Echocardiogram

Transthoracic echocardiography is the most available and efficient method for diagnosing PE and is useful for managing pericardiocentesis. PE can be identified on m-mode by the presence of an echo-free space between the epicardium and parietal pericardium; the presence in both systole and diastole suggests PE > 50 mL. Likewise, PE can be distinguished from pleural effusion by analyzing the parasternal window on 2D short-axis view, which shows the PE between the descending aorta and the heart. PEs are classified as small (50 to 100 mL), moderate (100 to 500 mL), or large (> 500 mL).

On the echocardiogram, signs of cardiac tamponade include "swinging heart", diastolic collapse of the right atrium and ventricle, left atrial compression, increased respiratory changes in tricuspid and mitral flow velocities, and inferior vena cava regurgitation.[19]

Tomography and cardiac magnetic resonance imaging

Tomography and cardiac magnetic resonance imaging (CMRI) are quite useful in the differential diagnosis of PE. They may show enlargement of the inferior vena cava and hepatic veins, compression of the cardiac chambers, septal bounce, and reflux of contrast material into the azygos vein or inferior vena cava. These methods can also be used to evaluate pericardial thickening or calcifications, cysts, and masses, as well as to provide information on the possible nature of PE based on attenuation measurements. On CMRI, hemorrhagic fluid is characterized by low intensity signals on T1-weighted images and high intensity signals on cine images with steady-state free precession.[12,19,20]

Other imaging methods

Right-sided cardiac catheterization contributes to the diagnosis of cardiac tamponade because it provides important information, such as increased right atrial pressure and equalization of pressures between multiple chambers (right atrium, right ventricle, and pulmonary capillary wedge pressure).[21]

The diagnosis of effusive-constrictive pericarditis is made when right atrial pressure does not fall by 50% or to a level lower than 10 mmHg after pericardiocentesis, when other causes that may elevate right atrial pressure, such as right ventricular failure or tricuspid regurgitation, have been excluded. Such condition may be found in patients undergoing radiation.

Cytological study

In patients with suspected malignant PE, cytological evaluation of pericardial fluid helps to diagnose the condition.[22] Pericardial biopsy (PB) with fluid cytology helps to reach a definitive diagnosis in 48% to 93% of cases.[23,24] However, a negative result does not rule out malignancy, given that PB typically analyzes only one sample, which could be a false negative, and results also depend on the experience of the examiner. PB can be performed through subxiphoid pericardiostomy (window) or pericardioscopy; the latter directly evaluates the pericardial space, increasing the sensitivity of the biopsy.[5,25]

Immunohistochemistry (IHC) staining in combination with clinical and morphological characteristics provides a more specific diagnosis, which may eliminate the need for more invasive tissue sampling. IHC allows differentiating between a mesothelial or epithelial origin of isolated atypical cells and cell clusters, in addition to identifying the primary site of malignancy in patients with a history of multiple malignancies or a previously unidentified primary site.[26]

Treatment

There is currently no defined treatment for PE in patients with cancer.[2,27] The presence of PE portends a worse prognosis, and treatment depends on the underlying cancer.[28,29]

In patients with cancer with PE and no secondary pericardial implants, the treatment should focus on the malignancy, with indication for pericardial intervention in symptomatic cases

(especially chest pain) and in patients with hemodynamic instability and signs of cardiac tamponade.[30-32] Many patients with cancer-related PE are asymptomatic and do not require specific treatment for PE.[33,34]

Surgical treatments in patients with cancer include pericardiocentesis, prolonged catheter drainage, pericardial window, and pericardiectomy.[15,35-39] In cases with recurrent PE or cardiac tamponade, pericardial window is an interesting option.[15,38,39] It involves creating a real window by a partial pericardiectomy, thereby creating a channel to allow for long-term drainage to an adjacent space, usually the pleural cavity.[40]

For patients with recurrent PE requiring multiple approaches, some options are possible. Intrapericardial instillation of cytostatic/sclerosing agents can be considered in the management of malignant PEs.[35,36]

Several components have already been evaluated for pericardial instillation, such as tetracyclines, bleomycin, and sterile talc powder. These drugs rapidly form pericardial adhesions that obliterate the pericardial space and control effusion recurrence .[37] Despite the high success rate of these interventions, with a good safety profile and low morbidity,[36] the side effects resulting from chemical pleurodesis still limit their routine indication. The main side effects result from induced inflammation, which can lead to fever, pleuritic chest pain, and atrial fibrillation.[15,36-39]

Conversely, pericardial injection of drugs, although effective for pericardial tamponade and recurrent PE, can only relieve symptoms temporarily.[40]

Systemic chemotherapy is effective for lymphoma and small cell lung cancer, which are sensitive to chemotherapy drugs. Immunotherapy has recently shown promising results in the treatment of neoplastic PE, constituting a new treatment option for these patients.[40]

Another possible line of treatment is immunomodulatory monoclonal antibodies against vascular endothelial growth factor receptors. Several recent studies have reported that, in patients with malignant PE, bevacizumab appears to be more effective than conventional chemotherapy drugs such as platinum and sclerosing agents.[41,42]

The indication for radiotherapy is extensive pericardial infiltration of encapsulated or unresectable cardiac tumors, such as mediastinal tumors.[40]

Pericardial disorders and risk of cancer

Some studies have drawn attention to an increased risk of cancer in patients diagnosed with pericardial conditions.[8,42,43] In a population-based cohort study using data from the UK Clinical Practice Research Datalink, pericarditis was associated with an increased subsequent risk of cancer (HR 3.03, 95% CI 2.74-3.36), and this association was particularly evident within 3 months of pericarditis diagnosis.[8]

In a Danish national cohort study, of 13,759 patients with acute pericarditis, 1,550 were subsequently diagnosed with cancer during follow-up. The cancer incidence rate was 1.5 (95% CI 1.4-1.5), with increased rates of lung, kidney, and bladder cancer, lymphoma, leukemia, and unspecified metastatic cancer.[43]

It is unclear whether this finding is related to an etiologic misdiagnosis of pericarditis in the presence of PE. Therefore, it seems reasonable to justify investigations focused on patients with cancer who present with pericarditis/PE in combination with advanced age, obesity, and need for hospitalization.

Author Contributions

Conception and design of the research: Fernandes F, Luzuriaga GDCJ, Dabarian A, Fernandes ID, Celano PM, Valsi IP, Fernandes FD, Madrini Junior V, Mello D, Freitas Jr AF, Santiago JAD, Queiroz CM; Writing of the manuscript: Fernandes F, Dabarian A, Fernandes ID, Celano PM, Valsi IP, Fernandes FD, Madrini Junior V, Mello D, Freitas Jr AF, Santiago JAD, Queiroz CM; Critical revision of the manuscript for important intellectual content: Fernandes F, Luzuriaga GDCJ, Dabarian A, Freitas Jr AF

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Review Article

Obstructive Cardiac Tumors

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Abstract

Cardiac tumors are considered rare clinical entities and can affect any cardiac tissue. Metastatic (secondary) cardiac tumors are more frequently diagnosed than primary tumors (malignant or benign). Both types can cause valve and/or inflow and outflow tract obstructions in any cardiac chamber, leading to symptoms of heart failure, as well as embolization and arrhythmia. Treatment of benign tumors is usually surgical, and that of metastatic and primary malignant tumors will depend on their origin and type, with poor prognosis. Recurrence of benign tumors is frequent. The aim of this article is to provide the clinician with tools to optimize diagnosis, differential diagnosis, and treatment of tumors with obstructive features causing heart failure.

Introduction

Cardiac masses are a frequent finding in clinical practice, encompassing a wide range of presentations, such as tumors, thrombi, vegetations, and anomalous structural changes.[1,2] Cardiac tumors, the type of mass to be discussed in this paper, can be divided into primary and secondary. Primary tumors are very rare, with a described incidence of 1.38/100 million individuals[3] and less than 1:2,000 autopsies.[1] It is estimated that 90% of these tumors are benign and originate from the myocardium or pericardium, consisting mainly of myxomas in adults and rhabdomyomas in children.[4] Malignant primary tumors, in turn, consist mainly of sarcomas, followed by lymphomas.[3] Secondary tumors (metastases) are malignant per se and have a higher incidence than primary tumors.[5]

Keywords

Heart Failure; Heart Neoplasms; Echocardiography; Magnetic Resonance Spectroscopy; Diagnostic Imaging.

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Cardiac tumors may be incidental findings, which has become increasingly more frequent in the last decade with advances in imaging methods.[6] They may be asymptomatic or lead to systemic manifestations, embolisms, and cardiac structural impairment. Depending on tumor location and size, the most frequent symptoms are dyspnea, chest pain, hypotension, cyanosis, syncope, and arrhythmias. These symptoms result from mass effect, which interferes with function of cardiac structural and with coronary or intracavitary blood flow.[7] The differentiation between benign and malignant tumors is important for prognosis, although it bears highlighting that even benign tumors may have important clinical repercussions, related to their location and size. The use of multimodality imaging is usually necessary to assess the etiology of cardiac tumors.[8] Mass location and aspect, image characteristics, and patient's age are some useful factors for diagnosis, which often rules out the need for biopsy. Obstructive cardiac tumors show a relatively predictable distribution in ventricles, atria, and valves, as presented in Figure 1.[9] It is worth emphasizing that the therapeutic approach should be individualized, considering factors such as possibility of tumor surgical resection, comorbidities, and prognosis of oncologic disease, in the case of secondary tumors. Therefore, treatment of cardiac tumors involves shared decision-making by the multidisciplinary team.[10]

This review focuses on the diagnosis and treatment of primary and secondary cardiac tumors whose clinical manifestation is associated with the hemodynamic obstruction caused by tumor, leading to heart failure, syncope, and shock. Pericardial and extracardiac tumors associated with cardiac compression and low cardiac output syndrome will not be approached.

Use of cardiovascular imaging for diagnosis of obstructive cardiac tumors

Intracardiac masses associated with shock, syncope, or low cardiac output require non-invasive investigation, avoiding invasive procedures such as tissue biopsy, if possible. Currently, multimodality imaging investigation allows for clarifying the etiology of most of these masses.

1) Transthoracic echocardiogram

a. Two-dimensional Doppler: widely available method, consisting of the front-line technique for diagnostic

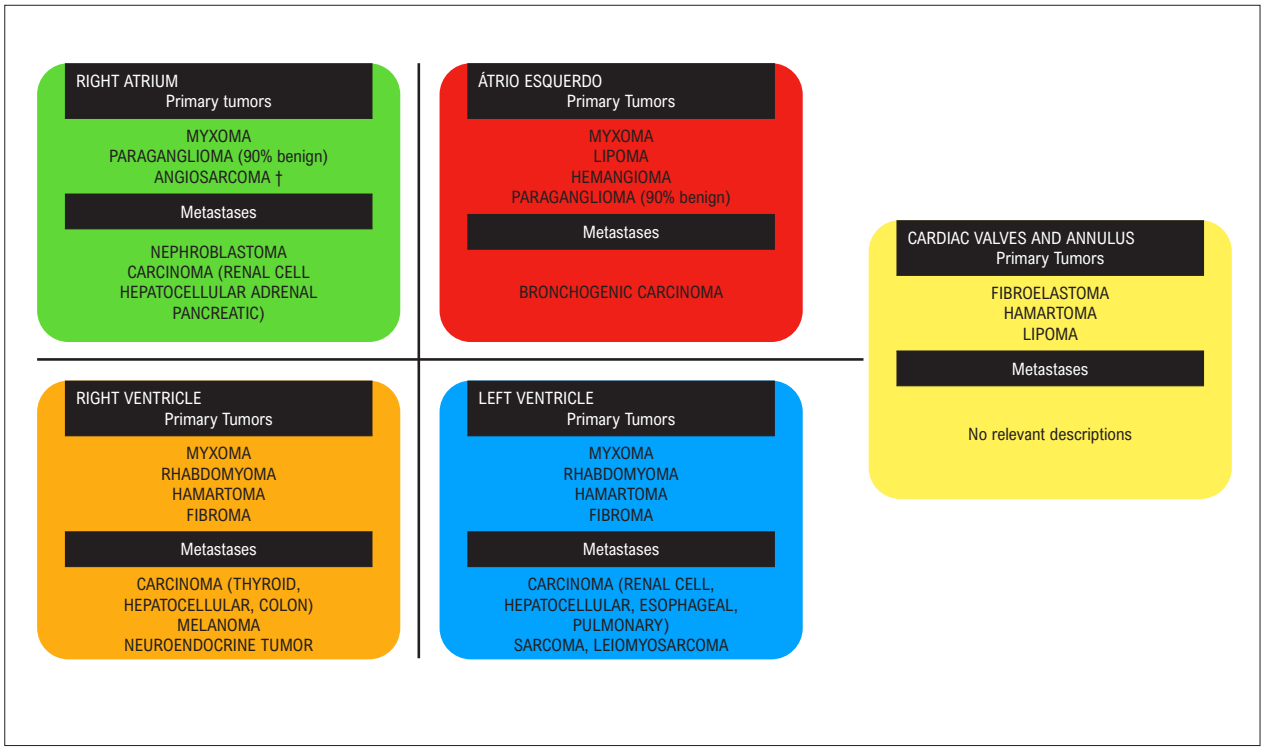

Figure 1 – *Specific location of the main obstructive cardiac tumors detected on transthoracic echocardiogram. Adapted from Griborio Guzman AG et al.* † *Malignant characteristic.*

investigation in suspected intracavitary mass. This test can determine tumor location, size, type of fixation, mobility, and hemodynamic consequences, in addition to assess the presence of pericardial effusion or other associated abnormalities. Furthermore, the use of Doppler allows for evaluating cardiac output and instant gradient between the chambers, important in cases of tumor obstruction (Figure 2). Its utility can be limited in patients with unfavorable acoustic window, such as obese patients, those with chronic obstructive pulmonary disease or subcutaneous emphysema, or in the investigation of masses coming from venae cavae or pulmonary branches.

b. Three-dimensional echocardiogram: it provides additional anatomical data for the spatial tumor characterization, which makes it possible to increase diagnostic accuracy of the method, help in surgical strategy, and monitor immediate and late outcomes of procedures.

c. Transesophageal echocardiogram: useful to supplement anatomical and functional assessment when the echocardiogram findings were not conclusive and for intraoperative assessment.

d. Contrast echocardiogram: malignant tumors, such as sarcomas, are highly vascularized, whereas benign ones, such as myxomas, are not. Thrombi, a very frequent and avascular condition, are the main differential diagnoses. Therefore, endocavitary contrast allows for characterizing the limits and the shape of masses, and also inform on the presence or absence of neovascularization surrounding the myocardium.[8]

2) Cardiac computed tomography

It has great accuracy for the anatomical definition of the tumor and its surrounding structures, enabling to assess the obstructive potential of these structures (Figure 3). Furthermore, it allows for complementary evaluation of coronary circulation, being useful in the assessment of concomitant obstructive coronary artery disease and possible surgical planning. Its use requires administering ionizing radiation and iodine contrast. Therefore, its use should be considered when other imaging tests were not conclusive.[8]

3) Cardiac magnetic resonance

This diagnostic method is essential in the etiologic definition of cardiac tumors and masses. It allows for tissue characterization, making it possible to define whether the content of the structure assessed is fat, fluid, fibrosis, or thrombus, for example. Assessment of cardiac tumor perfusion can define the magnitude of its vascularization, showing evidence of malignancy. It has excellent special/time resolution, allowing for an anatomical assessment of obstruction caused by tumor in the inflow and outflow tracts of cardiac chambers (Figure 4) and of intracavitary flows.[11,12]

4) PET/CT

Positron emission tomography-computed tomography (PET/CT) is a method that combines CT from radiology and PET scan from nuclear medicine in a single test and helps in tumor staging and in the assessment of recurrence and

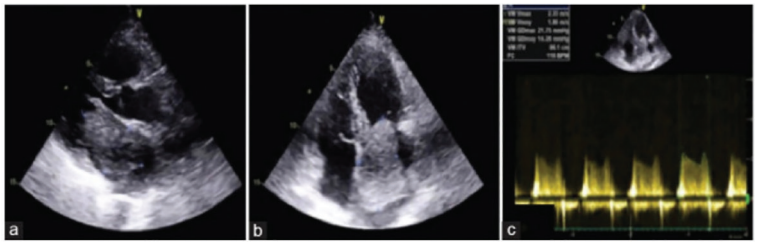

Figure 2 – *Giant left atrial myxoma in an adult at two-dimensional echocardiogram. A) Parasternal long axis view. B) four-chamber apical view. In both images, the tumor blocks the left ventricular inflow tract. C) Continuous Doppler showing increased mean gradient (14 mmHg) compatible with obstruction.*

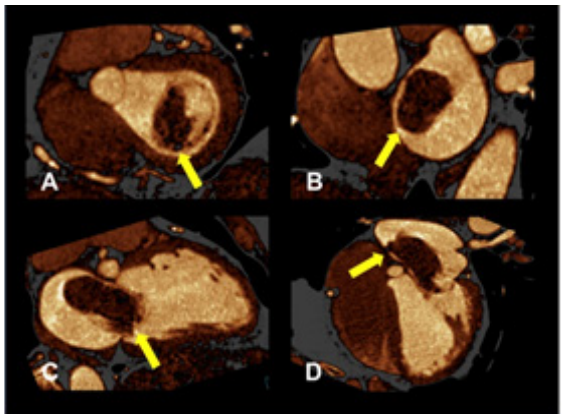

Figure 3 – *Cardiac computed tomography from a 58-year-old male patient evidencing myxoma on right and left atria (arrows). A,B) Short axis images of the left atrium revealing tumor protrusion into the mitral valve, partially blocking the left ventricular inflow tract. C) Two-chamber image showing the size of the mass in its larger axis. D) Four-chamber image of the heart in which is possible to observe a tumor pedicle adhered to the interatrial septum and the relationship between the mass and the mitral valve orifice. Image Courtesy of Dr. Tiago Augusto Magalhães.*

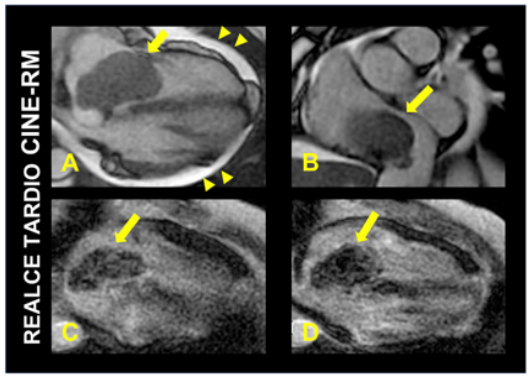

Figure 4 – *Cardiac magnetic resonance of 34-year-old female patient with a voluminous mass occupying the right atrium (arrows). A) Four-chamber cine magnetic resonance imaging scan showing a right atrial mass occupying part of the tricuspid valve plane during ventricular diastole and partially blocking the right ventricular inflow tract. This image also reveals discrete pericardial effusion (arrow heads). In B), short axis view of the right atrium depicts partial obstruction of inferior vena cava ostium by the atrial mass. C,D) Late enhancement images showing paramagnetic contrast uptake, which makes the diagnosis of intracavitary thrombus unlikely. Dynamic perfusion images of the mass (not shown) revealed signs of a highly vascularized structure, suggesting the diagnosis of malignant neoplasm. Image Courtesy of Dr. Tiago Augusto Magalhães.*

therapeutic response of several types of cancer. This test has no limitations with regard to acoustic window, metallic prostheses, and kidney failure.[8,13-16] PET/CT uses radiopharmaceuticals to define images, such as fluorine-18 fluorodeoxyglucose (^{18}F-FDG). The uptake of this substance by tumor cells reflects their metabolic activity and level of disease aggressiveness, helping to differentiate between malignant and benign tumors and thus avoiding cardiac biopsies and unnecessary invasive treatments.[12]

Secondary Obstructive Cardiac Tumors

Secondary cardiac tumors, such as cardiac metastases, are the most frequent cardiac tumors in clinical practice, being 22 to 132 times more common than primary cardiac neoplasms.[17,18] Cardiac metastases may occur by four routes: a) direct extension, b) bloodstream, c) lymphatic system (more frequent), d) intracavitary diffusion through the vena cava or pulmonary veins. Right cardiac chambers receive most of the lymph drained and are more affected by metastases. Secondary tumors are located on the myocardium, endocardium, or pericardium and can affect all ages.[19] Cardiac metastases may be found in up to 18% of individuals with stage IV cancer,[20] especially melanoma and lymphoma.[21] Thoracic neoplasms such as lung, breast, and esophagus cancer, are also among those more commonly associated with cardiac metastases.[18,22]

In most cases, cardiac metastases are clinically silent and diagnosed only on post-mortem examination.[10] When symptomatic, their main clinical manifestation is pericardial effusion, with varied degrees of severity. In tumors affecting the myocardium, infiltration and cardiac wall edema, causing arrhythmias, such as atrial fibrillation or flutter, and even atrioventricular block. Manifestations associated with systolic or diastolic ventricular dysfunction may occur, especially in patients with tumors with a diffuse ventricular involvement. Acute myocardial infarction is rare and may result from

thrombus or from perivascular or extrinsic compression. In tumors that disseminate through the vena cava, such as renal carcinoma and hepatocellular carcinoma, there may be complete right atrial obstruction and tricuspid valve block, resulting in a clinical pattern similar to that of pericardial constriction or myocardial restrictive disease.[20]

As previously highlighted, right cardiac chambers are the most involved in secondary tumors, with right chamber obstruction being one of the most severe presentations of metastatic tumors. These cases manifest with signs and symptoms of right heart failure, such as ascites, jugular swelling, lower limb edema, cyanosis, syncope, right bundle branch block, systolic ejection murmur along left sternal border, pulmonary hypertension, and even sudden death. Cases of pulmonary embolism secondary to tumor fragmentation and displacement[23-25] have already been described. Neuroendocrine tumors can be more associated with heart failure due to valve involvement, as occurs in carcinoid syndrome. A study reported the case of a metastatic nonfunctioning neuroendocrine tumor that caused outflow obstruction.[26]

There are numerous case reports of metastases causing ventricular outflow tract obstruction related to neoplasms of several primary sites, such as soft tissue sarcoma, lymphoma, leukemia, liposarcoma, ovary carcinoma, renal cell adenocarcinoma, hepatic tumors, pancreatic and colorectal adenocarcinoma, and even squamous cell carcinoma of the base of the mouth.[24,25,27-30]

Although less common, there are reports of left ventricular inflow (Figure 5) and outflow obstruction in individuals with synovial sarcoma of the foot and grade III pleomorphic leiomyosarcoma, both undergoing treatment with chemotherapy and radiation therapy and evolving to death after 3 and 6 months.[27] The main manifestation of left ventricular obstruction is progressive dyspnea. The masses can infiltrate ventricular wall and advance to the outflow tract, causing flow restriction. Similar presentations were also described in an individual with clear cell carcinoma; even after surgical removal of the mass, the patient died after 1 month.[31]

One of the most important invasive diagnostic methods is pericardioscopy, which allows inspection of the pericardium and epicardium and permits tissue acquisition. It is a powerful diagnostic tool, especially in diseases of unknown origin, particularly when combined with pathological and molecular methods.[10] In cases of right ventricular obstruction, the use of a Swan-Ganz catheter may be useful, and catheterization may allow for tumor biopsy, although the procedure carries a non-negligible risk.[25] The treatment of secondary cardiac tumors depends on the analysis of complications and clinical manifestations associated with the presence of cardiac metastasis, prognosis, and patient's functional status,[32] with no specific guidelines for each situation. Hemodynamically significant arrhythmias should be treated with cardioversion and radiofrequency ablation, when indicated. In cases of advanced blocks, implantation of a pacemaker may be necessary. Surgical treatment should be considered in the following cases: a) prognosis is favorable; b) no involvement of other metastatic sites; c) when the tumor can be completely removed; or d) in the presence of obstructive tumors. Adjuvant chemotherapy and/or radiation therapy should be performed together, according to tumor specificity.[10]

For obstructive tumors, more aggressive measures are often necessary to ensure hemodynamic stability. Treatment strategies such as placement of prostheses (stents) on the right ventricular outflow tract in a patient with metastatic sarcomatoid carcinoma and emergency surgery with or without pulmonary and/or tricuspid valve repair followed by neoadjuvant chemotherapy have already been described.[23-25] In many cases, cardiac metastases are found in already disseminated tumors, in which palliative treatment with

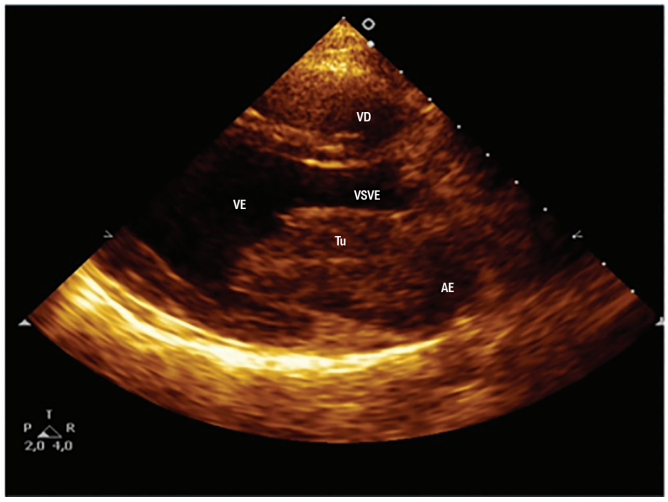

Figure 5 – *Transthoracic echocardiogram (parasternal longitudinal view). Tumor metastasis (osteosarcoma) originating from the right superior pulmonary vein and extending to the left atrium and protruding into the left ventricle. LA: left atrium; LV: left ventricle; Tu: tumor; LVOT: left ventricular outflow tract; RV: right ventricle. Image created by the authors.*

chemotherapy and/or radiation therapy is one of the only alternatives. The prognosis is usually poor, with death occurring in less than 6 months.[25,27-29,31,33]

Primary cardiac tumors

Cardiac tumors are rare (0.001% to 0.3%, according to pathological studies), and are classified as benign or malignant, and as primary or secondary (metastatic).

Secondary tumors occur more frequently. They have a variable location (myocardium, endocardium, and pericardium), different histopathological characteristics, can affect all ages. Furthermore, their clinical manifestations depend on location and hemodynamic involvement.[19]

In the pediatric population, most cases have a benign pattern and a satisfactory prognostic evolution. The primary benign tumors with greater prevalence and obstructive potential are, in an increasing order of frequency, rhabdomyomas, teratomas, fibromas, and myxomas.

Malignant tumors occur in nearly 10% of the cases and show an aggressive pattern, with limited prognosis and high mortality rates. Additionally, the most prevalent primary subtype is rhabdomyosarcoma.[34]

Benign primary tumors

Rhabdomyoma – The most common primary cardiac neoplasm in children, accounting for more than 60% of cardiac tumors in this population. Nearly 75% of the cases are diagnosed in the first year of life, mostly in the prenatal (through fetal echocardiography) or neonatal periods. It may be asymptomatic or manifest with signs of blood flow obstruction, as well as myocardial function involvement and arrhythmias. There is a strong correlation between cardiac rhabdomyoma and tuberous sclerosis, since this disease is present in 50% of children with the tumor, which may be ser unique or multiple.[19]

Rhabdomyoma has a biphasic growth pattern, with a progressive increase up to the beginning of the third trimester of pregnancy and total or partial regression up to the first year of life, which is why management tends to be conservative, unless the patient shows signs of cardiac decompensation. Rhabdomyoma is a non-infiltrative, non-metastasizing tumor usually located in the ventricles, especially in the septal region, and may cause fixed or dynamic obstruction of inflow or outflow tracts.[35]

Teratoma – Although rare, it accounts for 2/3 of pediatric cardiac tumors and is usually diagnosed in the fetal period. It is commonly located next to base vessels, and causes pericardial effusion and local myocardial impairment, which may lead to fetal or sudden death.

As well as other teratomas, cardiac teratoma is a solid mass with cystic and neuroepithelial components.[7,19]

Fibroma – This type of tumor may be associated with Gorlin syndrome, is mostly located in the septum or in the ventricular free wall, is usually nodular and solitary, can be well or poorly delimited, can present with calcifications or not, and has no tendency to regression. Treatment is surgical and involves complete resection, but it not always possible, due to tumor size and infiltrative aspect, which may lead to indication of heart transplantation.[7,34]

Myxoma – It is more common in adults, but may also occur in older children, and is often associated with genetic syndromes (LAMB, NAME and Carney) and endocrine diseases (adrenal hyperplasia, gigantism, and testicular Sertoli cell tumor).

It is mainly located in the left atrium, adhered to atrial septum or adjacent to the oval fossa, are typically pedunculated, and may also originate from the ventricular wall or from cardiac valves in variable proportions (Table 1).[9]

It may have an atrioventricular obstructive clinical pattern and cause embolic phenomena (paradoxical embolism) both for the pulmonary artery tree and for its periphery or the brain vascular territory, depending on the affected side (often the left one). It can also manifest with arrhythmias and signs and symptoms of decompensated acute heart failure, which brings potential risk of death.

Differential diagnosis is made with organized thrombus and with inflammatory diseases, due to the possibility of manifesting with constitutional symptoms resulting from cytokine release. It requires immediate diagnosis and surgical resection, due to the high risk of embolization (observed in up to 1/3 of patients).

Transthoracic echocardiogram is the initial diagnostic method, and transesophageal echocardiogram is the one with the highest sensitivity (95% vs. 100%). Cardiac magnetic resonance is a supplemental method that provides excellent tissue characterization and allows for identifying local invasion, in addition to permitting differentiation between myxoma and other types of tumors. PET /CT may be useful in differentiating malignancy and diagnosing neuroendocrine tumors. The prognosis of myxomas is excellent when they are treated with immediate surgical resection. Overall rates of survival are similar to those of the general population with the same age, although studies found a rate of postoperative recurrence from 1% to 6%.[7,9,34]

Primary malignant tumors

They are rare and show poor prognosis. Sarcomas are the most prevalent ones, although germ cell tumors, rhabdoid tumors, and lymphomas have also been described.[34]

Table 1 – Frequency of myxomas and their distribution according to cardiac chambers

Myxomas	Frequency (%)
Right atrium	12.7-28.0
Left atrium	60.0-90.0
Biatrial	1.3-8.5
Left ventricle	0.6-4.0
Right ventricle	1.7-8.0
Multifocal	0.8-1.6

Rhabdomyosarcoma - This is the most prevalent sarcoma subtype in the pediatric population, accounting for nearly 4 to 7% and often affecting cardiac valves. Clinical presentation is associated with the invasive or obstructive nature of the tumor, whose semiological characterization is difficult, due to its rapid growth. Nearly 46% of patients have metastatic disease at the time of diagnosis, which disseminated either via lymphatic system or by contiguity, and pulmonary artery tree obstruction is a manifestation to be considered. Treatment involves surgery, chemotherapy, and radiation therapy and is limited by tumor aggressiveness, thus resulting in low survival rates, which are below 1 year in most cases.[7,34]

Conclusion

This review about obstructive intracardiac tumors showed that their incidence is low, but they should be considered in patients diagnosed with intracardiac masses and showing hemodynamic impairment compatible with low cardiac output. In adults and children, myxoma stands out as the most common benign tumor, whereas tumor metastases (especially from melanomas and lung, kidney, and colon cancers) characterize the most frequent malignant cases and have limited prognosis.

Echocardiogram is still the most traditional diagnostic imaging method, providing the initial characteristics of the mass under investigation. Other methods, such as cardiac magnetic resonance, may be used in additional investigations. Special attention should be given to patients that have already been diagnosed with certain types of cancer and who evolve with progressive dyspnea.

In addition to frequent causes, such as anemia, differential diagnoses with obstructive intracardiac tumor should be considered as effects of chemotherapy, sarcopenia, ventricular diastolic or systolic dysfunction, pulmonary embolism, and restrictive syndromes. Treatment can be curative, such as in myxomas, or palliative, always considering the prognosis of the initial primary tumor.

Author Contributions

Conception and design of the research, Acquisition of data and Coordination: Cauduro SA, Dutra JPP; Writing of the manuscript: Cauduro SA, Dutra JPP, Fernandes F, Bonatto M, Santos MVC, Rocha LSO, Mialski TR, Nobrega APK, Brandão SCS, Barberato SH; Critical revision of the manuscript for important intellectual content: Cauduro SA, Dutra JPP, Fernandes F, Brandão SCS, Barberato SH.

Potential conflict of interest

No potential conflict of interest relevant to this article was reported.

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Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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Review Article

Takotsubo Cardiomyopathy in Patients with Cancer

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Abstract

Takotsubo cardiomyopathy (TC) in cancer patients has been predominantly noted as a cardiotoxic complication of oncologic therapy or secondary to catecholamine overload in specific tumors such as pheochromocytomas. The underlying pathophysiological mechanisms that lead to TC are not entirely understood. The diagnosis of TC can be challenging and may be neglected during cancer treatment, given the wide range of cardiotoxic effects of antineoplastic therapies. However, TC in oncology exists more often than formerly assumed, and it should be included in the differential diagnosis by physicians dealing with cancer patients. An increased suspicion is crucial for earlier diagnosis and treatment to improve outcomes. In addition to a risk model strategy identifying those cancer patients with the highest risk of having TC, translational studies are awaited. They would clarify the underlying mechanism of TC, disclose targets for prevention and treatment and determine whether re-exposing the patient to the same or equivalent anticancer agents would be secure and feasible.

Introduction

Takotsubo cardiomyopathy (TC) is a form of acute heart failure, characterized by regional dysfunction of the left and/or right ventricle, usually reversible, caused in most cases by acute physical or emotional stress in the absence of obstructive coronary artery disease. In 2006, the American Heart Association classified it in the group of acquired cardiomyopathies, under the name of stress-induced cardiomyopathy.[1] Subsequently, in 2018, the European Society of Cardiology (ESC) updated its diagnostic criteria, including pheochromocytoma as a specific cause of TC and the possibility of coexistence of coronary disease and TC.[2]

The main manifestations of TC are chest pain, dyspnea, electrocardiographic changes of ischemia, slight increase in cardiac enzymes and segmental ventricular dysfunction.[3]

Keywords

Takotsubo Cardiomyopathy; Neoplasms; Cardiotoxicity

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Cancer patients have many stressors and pathophysiological factors in common with patients with TC. This relationship has recently been described in the medical literature, and patients who develop TC with a previous history of cancer or active disease have a poorer prognosis.[4]

Nowadays, TC has been considered as an epiphenomenon of cardiotoxicity in patients with cancer.[5] Some chemotherapeutic agents, molecular-targeted agents and immune checkpoint inhibitors (ICI) can be linked to TC. It is known that the cardiovascular toxicities associated with the oncologic treatment have a broad spectrum, and chemotherapy-induced TC is a rare but acknowledged phenomenon of this spectrum.[5]

The objective of this article is to review the association between cancer and TC and to propose a rational clinical follow-up for cancer patients regarding the prevention and treatment of TC.

Epidemiology

TC incidence in cancer patients is equivalent in men and women, while there is an apparent predisposition for women in the general population.[6] Cancer and TC co-exist more frequently than formerly thought. Oncological patients have a higher incidence of TC than the noncancer population, with a mean incidence of about 53 in 100.000 chemotherapy-related hospitalizations versus 20.4 in the general population.[7]

Recent evidence shows that the prevalence of neoplasms is boosted in patients with TC compared to people of the same age and sex without the syndrome ranging around 4-29%, both at the time of diagnosis and during follow-up.[8,9]

TC can simulate an acute coronary syndrome (ACS) initially, with very similar constellation of signs and symptoms, and similar changes in electrocardiogram and cardiac enzymes, representing a challenging diagnosis. In fact, up to 6% of patients with an initial diagnosis of ACS in the emergency room have a final diagnosis of TC.[10] There are two models of clinical presentation of this syndrome, shown in Table 1.

The secondary TC model has epidemiological aspects that differ from the primary model: a higher prevalence in men, reaching 50% in some studies, with the most comprehensive age group, generally above 40 years. It usually develops after a few days of hospitalization.[11] The differences are shown in Table 2.

TC in cancer patients usually has the secondary type of presentation, as a cardiac complication in patients submitted to multi-drug treatments for cancer during hospitalizations.[12]

It has been shown that patients with solid tumors are more likely to TC than those with hematologic malignancies. Breast

cancer, followed by tumors of the gastrointestinal system and respiratory track the most common malignancy associated with TC.[8,9,13,14]

In a large US cohort study that analyzed more than four million inpatients with active cancer, the prevalence of TC in these patients was 12%. The investigators also examined the association between primary tumor type and the risk for TC. They found that only breast and lung cancer were associated with a significant chance of TC.[13] Furthermore, TC appears to be more prevalent among patients with advanced or recurrent disease.[14]

The first Brazilian TC registry, REMUTA (Takotsubo multicenter registry), has included 169 patients admitted with primary or secondary TC. An incidence of 14.7% of patients with a previous or current cancer diagnosis was observed.[15] Figure 1 shows a high rate of complications in patients hospitalized with TC in the REMUTA registry, and these complications were more common in patients with secondary Takotsubo.

Pathophysiology

There are several proposed pathophysiological mechanisms responsible for TC, with activation of the sympathetic nervous system and coronary vasospasm as the main ones.[5]

The triggers of TC in cancer are various. Cancer patients are constantly under stressors that increase the risk of developing TC. First, the emotional stress that a cancer diagnosis and its treatment impose to patients can increase the adrenergic load. Additionally, patients are frequently submitted to the physical stress of surgeries and diagnostic procedures, and to pain, and some physical complications of chemotherapy such as anemia, and dehydration that may lead to hyperkinesia.[4,16-21]

These causative and predisposing factors explain the "multi-hit hypothesis" for TC in cancer patients.[22]

Figure 2 illustrates the pathophysiological mechanisms involved in takotsubo cardiomyopathy in cancer patients.

Diagnosis and management

Chest pain or dyspnea during or after anticancer treatment is the typical clinical presentation of TC, however in 26.8% of patients, cardiogenic shock may be the first and potentially fatal manifestation.[23,24]

Further complications comprise respiratory failure, pulmonary edema, arrhythmias, cardiac thrombus, or cardiac arrest.[14]

The median time of TC onset is two days (1–150) after the beginning of treatment,[23] and diagnosis using available TC criteria has been suggested.[25,26]

Investigations in a patient with cancer with presumed TC should include clinical examination, ECG, transthoracic echocardiography, cardiac biomarkers, and cardiac magnetic resonance as show in Figure 3.[25,27,28]

Table 1 – Models of clinical presentation of Takotsubo cardiomyopathy

Takotsubo cardiomyopathy clinical presentation model	
Primary	Acute cardiac symptoms are the primary cause of seeking medical care
Secondary	Occurs in patients already hospitalized for reasons other than cardiac. It is a complication of the primary condition or its treatment. It is the most frequent model in cancer patients.

Table 2 – Differences between primary and secondary Takotsubo cardiomyopathy[11]

	Primary TC	Secondary TC
Presentation	On emergency admission	Mostly hospitalized, during postoperative or intensive care
Diagnosis	Rapid, based on the history of chest pain and dyspnea, abnormal electrocardiogram and/or elevated troponin and echocardiogram with typical alteration. Urgent catheterization almost always confirms the diagnosis by excluding ACS	Usually made after the patient presents clinical worsening, hemodynamic instability, arrhythmia, signs of heart failure. Catheterization is performed in a much smaller portion
Gender	90% women	50% women
Age	> 60 years	> 40 years
Complications	Few, mild and transient	High incidence of shock, mechanical ventilation, use of vasoactive amines and mechanical circulatory support
In-Hospital mortality	Low: around 5%	High: can reach 30%

TC: Takotsubo cardiomyopathy; ACS: acute coronary syndrome.

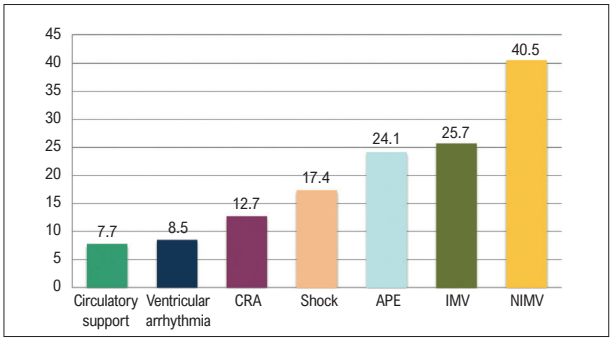

Figure 1 – *In-hospital complications in Takotsubo cardiomyopathy in the REMUTA registry. CRA: cardiorespiratory arrest; APE: acute pulmonary edema; IMV: invasive mechanical ventilation; NIMV: non-invasive mechanical ventilation.*[15]

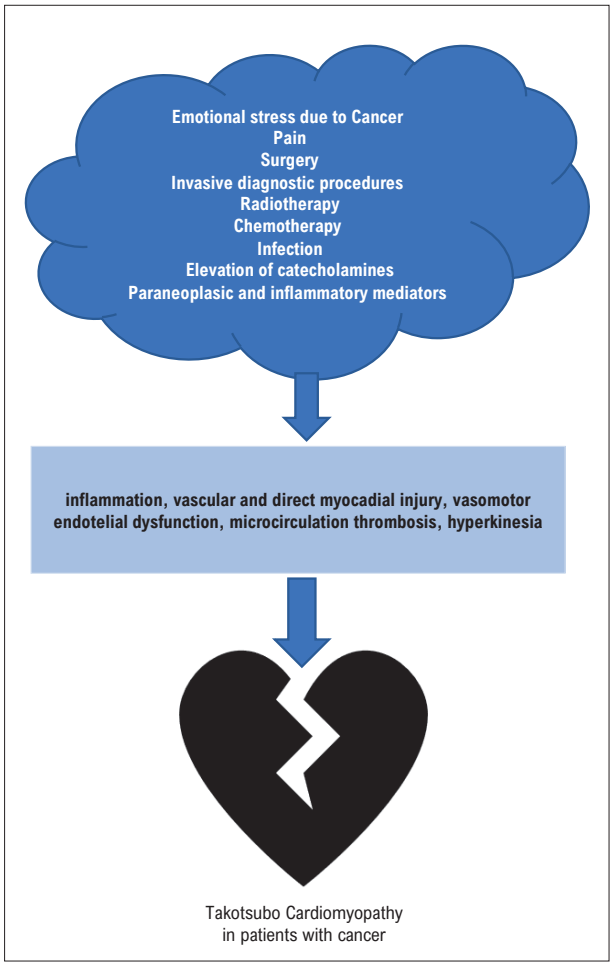

Figure 2 – *Potential triggers and proposed pathophysiological mechanisms involved in takotsubo cardiomyopathy in cancer patients*

The diagnostic criteria for TC are shown in Table 3. It should be noted that in 2018, the ESC updated this classification, including two important changes: the inclusion of pheochromocytoma as a cause of TC and the exclusion of coronary artery disease as an exclusion criterion, provided that the change in contractility extends beyond the affected coronary territory.[25] Also, the acute coronary event itself can trigger TC.[28]

Most patients need invasive coronary angiography to exclude acute myocardial infarction. In patients with advanced malignancy or significant thrombocytopenia where invasive coronary angiography is contraindicated, a coronary computed tomography angiography is advised. Cardiac imaging studies should be conducted as early as feasible when the diagnosis is presumed, as left ventricular dysfunction (LVD) can be transient. If substantial LVD is seen, repeat imaging is recommended to confirm recovery.[28]

Nuclear magnetic resonance is an important diagnostic tool, especially in cases where myocarditis needs to be ruled out as a differential diagnosis or in cases of focal TC, with respect to the coronary territory, to assess whether the pattern of delayed enhancement is typical of ischemic disease or not. Enhancement may be present in a minority of patients – fragmented and not typical for coronary artery disease but absent in most cases. In addition, it accurately quantifies left ventricular and right ventricular function, and detects complications (thrombi, pleural and pericardial effusion).[26]

In addition, interruption of the anticancer drug treatment in patients with Takotsubo syndrome is suggested, and QT-prolonging drugs should be avoided.[25]

In cases of ICI-associated TC, the role of immunosuppression is unknown; if myocardial inflammation is present in a TC pattern on cardiac magnetic resonance, then intravenous methylprednisolone is recommended given the overlap between ICI-induced TC and ICI-induced myocarditis. Limited information exists regarding the feasibility of ICI rechallenge following TC and after recovery of left ventricular function.[28]

A multidisciplinary team discussion is recommended after recovery from the acute phase of TC and, if restarting the cancer drug is necessary from an oncology point of view, cardiac follow-up is recommended.[28]

Chemotherapy and Takotsubo cardiomyopathy

TC usually occurs during oncologic treatment, and it is commonly attributed to the acute cardiotoxicity of the treatment mainly by free radicals-induced cardiac myocyte damage. The primary chemotherapeutic agents associated with TC are 5-fluorouracil, capecitabine, cytarabine, hydroxyurea, daunorubicin, cisplatin, docetaxel, paclitaxel.[29]

Among cancer patients exposed to these drugs, those with risk factors such as female sex, age more than 45 years, hypertension, dyslipidemia, anemia, lung and neurologic disease were more predisposed to develop TC.[5]

It is possible that an interconnection between different cancer stressors, inflammation, and cytokine synthesis in response to catecholamines, may explain the differences in the manifestations of TC in patients with cancer. Other oncologic treatments have also been linked to TC.[29]

Bevacizumab is associated with specific cardiovascular side effects, in particular arterial thromboembolism.[30] It was observed in animal models that a blockade in the vascular endothelial growth factor (VEGF) signaling pathway could dilate the ventricles and reduce the contractile function, leading to heart failure.[31]

Rituximab has also been shown to induce adverse cardiac events, including arrhythmia and less frequently, myocardial infarction. Recently, it was documented acute ventricular dysfunction after infusion of rituximab, indicating that changes in the growth factor-β levels may have led to the formation of reticulin fiber (diffusely present in cardiac muscles), generating a reduction in myocardial contractility and conduction.[32] For monoclonal antibodies and immunotherapy agents it was demonstrated some putative cardiotoxic and pro-inflammatory effects of pembrolizumab associated with trastuzumab, and

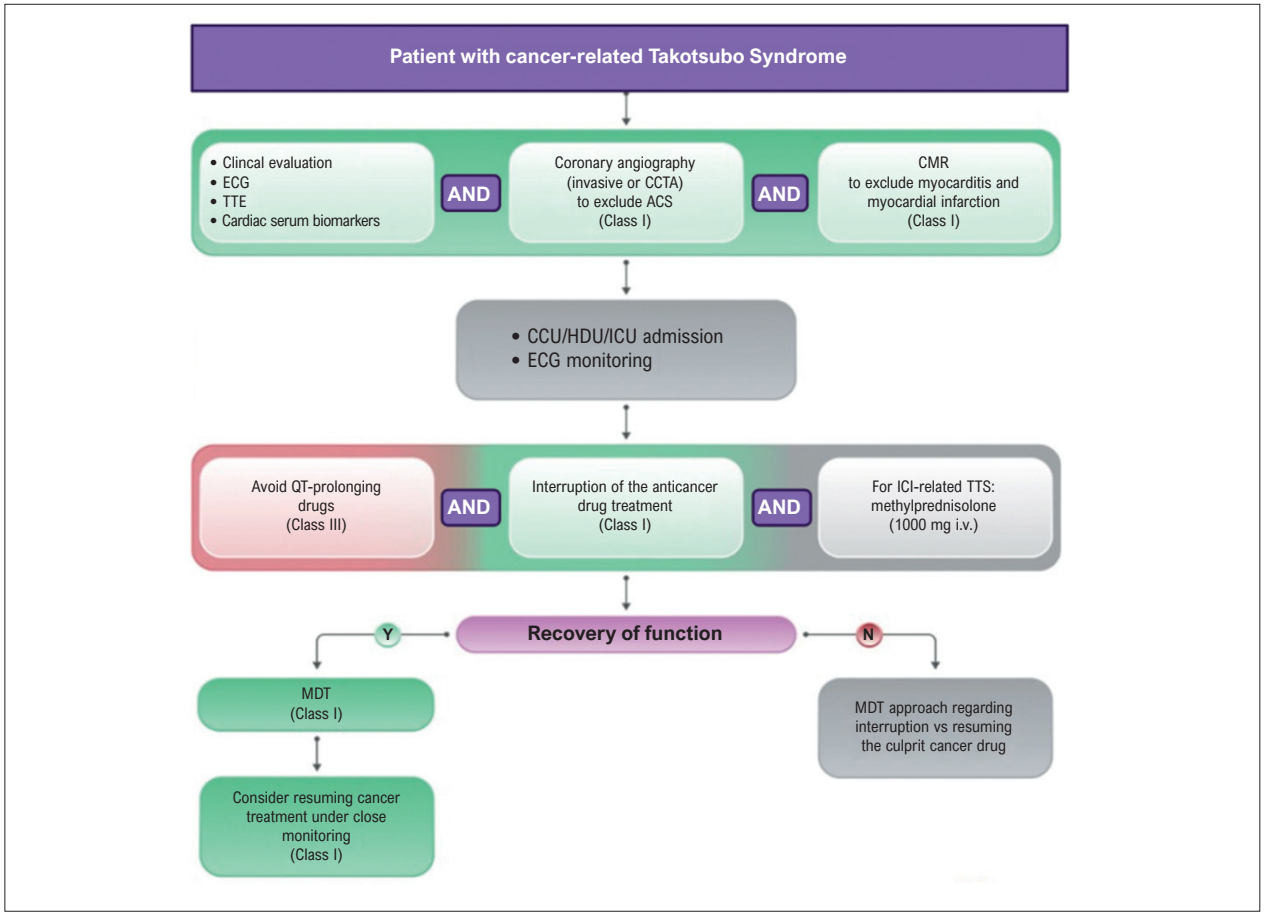

Figure 3 – *Diagnosis and management of cancer-related Takotsubo syndrome. ACS: acute coronary syndromes; CCTA: coronary computed tomography angiography; CCU: coronary care unit; CMR: cardiac magnetic resonance; ECG: electrocardiogram; HDU: high-dependency unit; ICI: immune checkpoint inhibitor; ICU: intensive care unit; i.v.: intravenous; MDT: multidisciplinary team; N: no; TTE: transthoracic echocardiography; TTS: Takotsubo syndrome; Y: yes.*[28]

Table 3 – Diagnostic criteria for Takotsubo cardiomyopathy[25]

1	Presence of transient left ventricular dysfunction. Associated right ventricular dysfunction may occur. Contractility abnormality extends beyond the territory of an epicardial coronary artery. In rare cases of focal TC, it may be restricted to one territory.
2	Physical or emotional stress often precedes the event but is not mandatory
3	Acute neurological disease and pheochromocytoma can be a trigger for TC
4	Acute electrocardiographic changes are almost always present, but in rare cases the electrocardiogram may be normal
5	Levels of cardiac biomarkers (CK or troponin) are often moderately elevated, as well as BNP
6	Significant coronary artery disease can coexist with TC
7	There can be no evidence of acute myocarditis

TC: Takotsubo cardiomyopathy; ECG: electrocardiogram; CK: creatine kinase; BNP: B-type natriuretic peptide.

it is possible that these effects could be mediated by overexpression of inflammatory related pathways.[33]

Clinical Implications

Cancer patients who develop TC have a poorer prognosis;[5,8] a meta-analysis evaluating clinical outcomes in this population has shown that patients that present both TC and cancer have higher probability of mechanical ventilation use, longer intensive care time stay and a 3-fold increase in the relative risk of clinical events comparing to patients with TC and no cancer.[8]

The RETAKO, a registry on TC, developed between 2002 and 2019 in 38 hospitals, included patients with history of any malignancy or tumor, even benign, that received

chemotherapy, radiotherapy or specific surgery, current or in the past. Any type of neoplasm was described in 129 (11.8%) in a cohort of 1097 patients with TC. The results showed that, during hospital stay, cancer patients suffered more complications, highlighting heart failure/shock, acute renal failure and a trend towards combined infections. On follow-up, they presented higher mortality and more combined MACE events, with a non-significant trend in cardiovascular recurrences or readmissions.[34] In the REMUTA registry, patients with TC and a previous or current history of cancer had a significantly higher in-hospital mortality than those with no cancer diagnosis (16% vs. 9%, $p<0.05$).[15]

TC in cancer patients can lead to interruptions in chemotherapy, which may adversely affect oncologic outcome. Additionally, cancer patients are at increased risk for developing TC while they are on active oncologic treatment with surgery, radiation and chemotherapy.[5]

Cancer patients should be carefully and closely monitored to identify those patients at greater risk of developing TC in order to make early diagnosis and efficient care.

Follow-up of patients with cancer and risk for developing takotsubo

Cancer patients at higher risk for developing takotsubo should have more rigorous clinical follow-up. The Brazilian cardio-oncology guideline recommends, ideally, a consultation with a cardiologist, and baseline tests such as ECG, laboratory tests (complete blood count, thyroid function tests, type B natriuretic peptide, kidney and liver function tests and cardiac troponin) and Echocardiogram and if possible, at three, six and 12 months. In addition to these general recommendations for cardiac follow-up of cancer patients, additional evaluations could be considered whenever the cancer patient is submitted to new diagnostic or therapeutic procedures during the oncologic treatment once they can trigger the appearance of TC.[35] In Figure 4, clinical follow-up for this population of higher risk is presented.

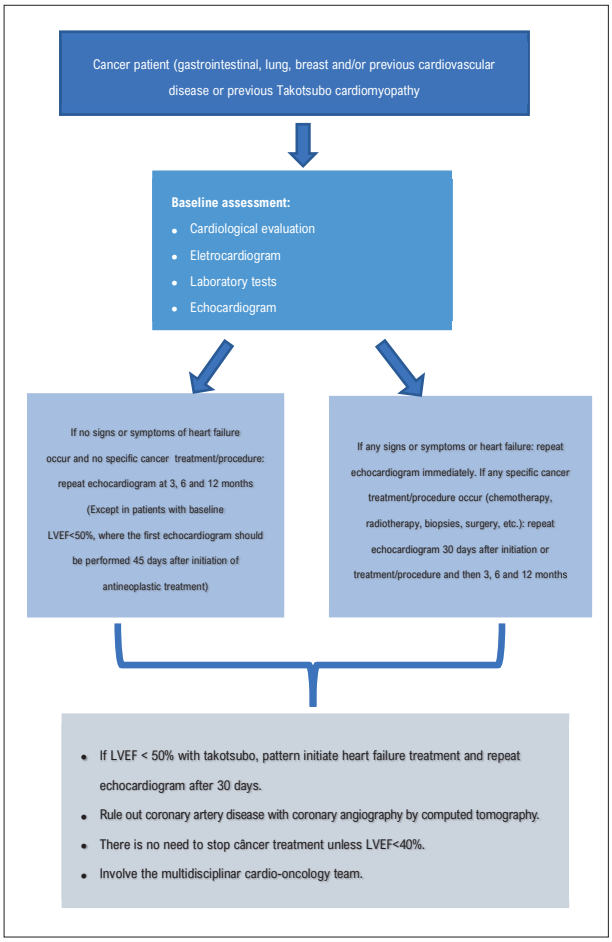

Figure 4 – *Clinical follow-up for cancer patients at higher risk of takotsubo cardiomyopathy. LVEF: left ventricular ejection fraction (original figure from the authors).*

Conclusion

Cancer patients are more likely to develop TC.[5] When this occurs, the prognosis is significantly worse than in patients without cancer, because in addition to morbidity, cancer treatment is often interrupted or modified, which can further worsen patient's clinical condition.[28] Strategies for rigorous clinical follow-up of patients at higher risk of developing TC may be implemented for a rapid diagnosis and effective treatment. A risk model strategy using modern data tools such as artificial intelligence and machine learning could help in identifying those cancer patients with the highest risk of having TC.[13] In addition, translational studies may bring some light to the understanding of the underlying mechanism of TC, disclosing targets for prevention and treatment, and whether re-exposing the patient to the same or equivalent anticancer agents would be secure and feasible.

Author Contributions

Conception and design of the research, Writing of the manuscript and Critical revision of the manuscript for important intellectual content: Macedo AVS, Almeida Junior GLG, Rehder MHHS.

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Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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Review Article

Right Ventricular Dysfunction in the Cancer Patient

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Abstract

Right ventricular dysfunction (RVD) is present in several clinical conditions, and its clinical impact and prognosis in cardiology has been more studied in recent years. In oncology, some studies have tried to determine the role of RVD in cardiotoxicity caused by some therapies including anthracyclines, trastuzumab, cyclophosphamide and dasatinib. In the present study, we made a literature review on the subject, trying to highlight the challenges for the coming years.

Introduction

The assessment of the right ventricle (RV) can be challenging due to its anatomical and functional features. Recently, more attention has been paid to the understanding of conditions that affect the RV, either alone or in combination with the left ventricle (LV), their clinical and prognostic impact, and to interventions that may reduce their clinical effects.

Cardio-oncology is a growing field with well-defined strategies for the detection, follow-up and prevention of cancer treatment-related cardiotoxicity. However, the RV is little mentioned in most guidelines that address cardiotoxicity. Recently, several studies have tried to establish the prevalence and the impact of right ventricular disfunction (RVD) in this context. In this paper, we will discuss some fundamental aspects of the mechanisms, clinical manifestations, and therapeutic approach of RVD, and summarize the main findings from studies evaluating the RV, either alone or in combination with the LV, in the context of cardiotoxicity. The prevalence, clinical impact and diagnostic methods to identify the involvement of the RV will be reviewed as well as the challenges that still exist in this scenario that has received growing attention in the last years.

Keywords

Right Heart Failure; Cardiotoxicity; Cardio-Oncology; Cardiac Dysfunction

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Right ventricular dysfunction

The increase in right ventricular afterload is the main pathophysiological mechanism of RVD, which may be caused by cardiac, pulmonary, and other diseases. Cardiac diseases of various etiologies have been related to RVD, including ischemic disease (myocardial infarction), myocarditis, takotsubo cardiomyopathy, dilated cardiomyopathy, hypertrophic cardiomyopathy, amyloidosis, Chagas disease, arrhythmogenic right ventricular cardiomyopathy (in which right ventricular myocardium is replaced by fibro-adipose tissue), Uhl's anomaly (which involves aplasia or hypoplasia of most of the right ventricular myocardium), Ebstein's anomaly (defined as apical displacement of the septal and posterior tricuspid leaflets, which induces severe tricuspid regurgitation), and congenital disease (Fallot, atrial septal defect with left-to-right shunt or pulmonary regurgitation). These encompass conditions that affect the RV only, others that affect predominantly the RV and also the LV in more severe cases, and others that affect both ventricles. Other causes of RVD include pulmonary thromboembolism, chronic obstructive pulmonary disease, pulmonary arterial hypertension (PAH), obesity, and sleep apnea.[1]

Clinical signs of RVD result mainly from systemic congestion (lower limb edema, jugular turgescence, congestive hepatopathy, ascites, edematous bowel loops). In severe cases, the right heart dilates and, due to interventricular dependence, can compromise left ventricular filling, reducing the performance of the LV and causing low cardiac output. The diagnosis is based on clinical history, physical examination and complementary tests, including electrocardiography (ECG) with axis deviation to the right, and signs of right ventricular hypertrophy, echocardiogram (ECHO), which is an easily accessible tool that provides important information, including assessment of right ventricular function by tricuspid annular plane systolic excursion (TAPSE) and signs of venous congestion, and cardiac magnetic resonance (CMR), which is the best method for evaluation of right ventricular function and etiological definition.[2]

The crucial role of the right ventricular function in establishing the prognosis in several diseases has been increasingly recognized. In general, RVD is associated with poor clinical outcomes, regardless of the underlying mechanism. Patients with heart failure (HF) and reduced left or right ventricular ejection fraction had an increased risk of mortality, urgent transplantation or urgent assist device placement compared to those without RVD.[3]

The initial evaluation of patients with RVD aims to assess the clinical severity and identify the causes of right ventricular failure, focusing on those that require specific therapy. The management of acute insufficiency of the RV requires not only the understanding of anatomical and physiological particularities of the RV, but also the rapid identification and treatment of underlying causes and related pathophysiological disorders.[4,5]

The objectives of RVD treatment include reduction of RV afterload, optimization of RV preload and possibly improvement of right ventricular contractility.[6] However, current evidence indicate that right ventricular afterload reduction is the most appropriate approach, especially in the scenario of PAH.[7]

Afterload reduction

Adaptive changes favor vasoconstriction, thrombosis and proliferation of endothelial cells in PAH, contributing to increased peripheral vascular resistance (PVR) and right ventricular afterload, disadaptive hypertrophy, and eventually RVD. Advances in the pharmacotherapy in the last two decades increased mean survival time from 2.8 years to approximately eight years after the diagnosis. Aiming to augment arterial vasodilation and inhibit platelet aggregation to reduce PVR, the treatment includes: (a) oxygen administration as appropriate, since hypoxemia increases pulmonary vasoconstriction; (b) prostacyclin agonists (epoprostenol, treprostinil, iloprost, selexipag); (c) endothelin receptor antagonist (endothelin 1, bosentan, ambrisentan, macitentan); (d) increase of nitric oxide production (sildenafil, tadalafil, riociguat); (e) calcium channel blockers (anlodipine, levamlodipine, nimodipine); (f) combined therapy.[8] In the randomized study AMBITION, the efficacy of the combination therapy with ambrisentan and tadalafil was evaluated in 605 patients, and compared with their use as monotherapy; there was a 50% reduction in the primary end point (death, hospitalizations for PAH, disease progression, unsatisfactory response to therapy) ($p<0.001$), and improvement in exercise capacity ($p<0.001$).[9] Based on results from this trial, the European Cardiology Society and the European Respiratory Society recommend the combination of ambrisentan and tadalafil as initial therapy for patients with PAH and symptoms class I or II (WHO (class I recommendation, level of evidence B. In addition, the guidelines recommend intravenous prostacyclin in functional class II patients with rapid disease progression or poor prognosis and functional class IV patients.[10]

Afterload optimization

RVD is frequently associated with increased overload, leading to dilation of the RV, tricuspid regurgitation, and congestion. In more severe cases, interventricular septal deviation may be seen towards the RV, with consequent reduction of left ventricular filling and low cardiac output. Therefore, optimization of blood volume to prevent right ventricular dilation is crucial and achieved by non-pharmacological measures (fluid and salt restriction) and diuretics, although there are no randomized study evaluating the benefit, type or dose of diuretics in the management of RVD.[8] High doses of loop diuretics (e.g. furosemide) are usually required, mainly due to concomitant neurohormonal activation, diuretic resistance and impaired absorption of medications related to visceral edema. Combined therapy of loop diuretics plus thiazide diuretics, aldosterone antagonist and/or acetazolamide may be needed. A common mistake is to believe that most patients with RVD are preload-dependent and should be treated with volume supplementation to promote elevated right ventricular filling and an ideal cardiac output; conversely, most clinical exacerbations are caused by right ventricular volume overload that causes systemic venous congestion, that may lead to cardiorenal syndrome and cardiac output reduction.[6]

Contractility increase

Contractility can be increased by inotropic agents or circulatory assist devices. Inotropic therapy is indicated for patients with acute HF and reduced cardiac output However, there are no studies investigating the efficacy of chronic inotropic therapy in right HF. Potentially beneficial inotropic agents include milrinone, levosimendan and dobutamine. Apart from an acute case of HF decompensation with low cardiac output, inotropes should be avoided in patients with right HF due to limited evidence of benefit and associations with increased mortality. Right ventricular assist devices are mechanical pumps that take over the right ventricular function and are used in refractory cases. Examples of these devices include Thoratec PVAD (Thoratec, Pleasanton, CA) and Impella RP (Abiomed,Danvers, MA) approved for temporary support of the RV for two weeks, and CentriMag up to four weeks. Thirty-day and one-year survival after implantation of CentriMag was 72,1% e 54,6%, respectively, in a retrospective study with 55 patients. Cardiac transplant, however, remain the definite therapy for refractory right ventricular failure.[8]

Right ventricular dysfunction in cancer patient

Cardio-oncology is an emerging area in cardiology aimed at protecting the cardiovascular system, reducing mortality, and improving the quality of life of cancer patients, and enabling them to receive the best treatment available without interruptions. Although position statements and guidelines on prevention and management of cancer-related and treatment-related cardiotoxicity address mainly the LV, the involvement of the RV has been a subject of intense research recently. Since the prognostic role of the structure and function of the RV has been proved in several cardiovascular conditions, such as HF, coronary artery disease, pulmonary hypertension and hypertrophic cardiomyopathy, the assessment of the RV in oncologic patients has gained space.[4]

Radiotherapy (RT) to the chest area can damage the heart in a dose-dependent manner.[11] Evidence has shown that high-dose RT (>30Gy), combined with chemotherapy, may induce fibrosis and narrowing of right ventricular myocardium at long term.[12] Other potential pathophysiological mechanisms that could explain right ventricular remodeling include microvascular and macrovascular ischemia, accelerated atherosclerosis, and oxidative stress.[4]

Some anticancer drugs are known to cause PAH (e.g. dasatinib) and/or RVD (anthracyclines, trastuzumab, cyclophosphamide, and dasatinib).[13] We will now review important aspects and studies focusing on the effects of these interventions on the RV and their diagnosis.

Anthracyclines and Trastuzumab

Recent studies have shown structural changes and reduced right ventricular function during cancer treatment, especially with anthracyclines and trastuzumab.[14] Currently no guideline explicitly incorporates right ventricular parameters into the definitions of cancer therapy-related cardiac dysfunction (CTRCD).[15]

Although the mechanisms of right ventricular remodeling induced by chemotherapy have not been elucidated, the direct destructive effect of chemotherapy on the myocardium, oxidative stress, endothelial dysfunction and the negative impact of pulmonary circulation seem to significantly contribute to right ventricular failure.[16] The higher sensitivity of the RV to cancer therapy-related cardiotoxicity may be explained by the thinner structure of this ventricle, with fewer myofibrils.[17]

Most studies with analysis of the RV in cardio-oncology have involved breast cancer patients and childhood cancer survivors.[4] Evidence has suggested that the RV is affected as frequently as the LV,[4] and even earlier in some situations.[18] To confirm the possibility of assessing the RV to early detect subclinical cardiotoxicity and to define its criteria, larger studies, preferably multicentric ones, are still warranted.[18]

CMR and echocardiography are the techniques of choice to evaluate right ventricular systolic function in cancer patients.[16] CMR is the gold standard to assess right ventricular diameter and function.[4] There are few studies, with a limited number of patients, regarding right ventricular function following chemotherapy, but all studies agree that its ejection fraction reduces with anthracyclines in adults who had survived childhood cancer,[19,20] and with anthracyclines[21] and trastuzumab[4,22] in breast cancer patients.

An accurate evaluation of the RV by conventional echocardiography is still challenging.[18] Right ventricular shape and geometry limit the capacity of conventional echocardiographic indexes like right ventricular ejection fraction, fractional area change (FAC), and tricuspid annular plane systolic excursion (TAPSE), to reliably detect subtle changes in right ventricular systolic function in cancer patients.[4]

Right ventricular strain seems to be a reliable, robust and easy-to-use indicator in cardio-oncology.[4] Right ventricular global longitudinal strain (RVGLS) is the only index of systolic performance with consistent and homogenous data in oncological patients,[4] and apparently a better indicator of right ventricular function than the right ventricular free wall longitudinal strain (RVFWLS).[4] Shi et al.[11] recently published a systematic review and meta-analysis of 21 studies including 1355 patients, evaluating the RV by echocardiography at the beginning of treatment and follow-up of cancer patients who underwent chemotherapy and/or radiotherapy. The authors found an increase in pulmonary artery systolic pressure (PASP), as well as reductions in TAPSE, S', RVGLS and RVFWLS.[11]

Further studies are needed to determine the prognostic value of the assessment of the RV in oncologic patients.[23] In breast cancer patients receiving epirubicin, the decrease in the RVFWLS was significantly correlated with the development of dyspnea, regardless of systolic and diastolic function in both ventricles.[24] In patients with stage III non-small cell lung cancer receiving concurrent chemoradiotherapy, baseline RVFWLS and its variation was an independent predictor of all-cause mortality.[25]

Desatinib

Desatinib is an oral tyrosine kinase inhibitor approved as a first-line treatment in patients with chronic myeloid leukemia and acute lymphocytic leukemia. It induces endothelial cell damage, oxidative stress, and changes the proportion between proliferation and antiproliferation of the endothelial and pulmonary arterial smooth muscle cells, which leads to higher susceptibility to pulmonary hypertension.[16] In the DASISION (DASatinib versus Imatinib Study in treatment-Naïve chronic myeloid leukemia patients), 5.4% of patients randomized to desatinib were diagnosed with PAH, as compared with 0.4% in those randomized to imatinib.[26]

Symptoms of PAH are nonspecific, like dyspnea and fatigue. In more advanced stages, signs and symptoms of right HF may emerge. Echocardiography is the first choice to assess the risk of PAH in patients with suggestive symptoms and/or signs during cancer treatment. In patients with chronic myeloid leukemia treated with drugs that potentially cause PAH, treatment should be discontinued in case of signs suggestive of PAH (peak tricuspid regurgitation velocity > 3.4 m/s, corresponding to a pulmonary artery systolic pressure ≥ 50 mmHg) until the diagnosis is confirmed or ruled out by right heart catheterization.[27] Most patients have clinical and functional improvement after dasatinib discontinuation.[16]

Cyclophosphamide

Cyclophosphamide is an alkylating agent that interferes with DNA replication.[16] The metabolism of cyclophosphamide in the lungs is partially responsible for its pulmonary toxicity. Evidence suggests that cyclophosphamide and its metabolites cause peroxidation of cell membrane lipids.[28]

A systematic review of the role of alkylating agents in the development of pulmonary hypertension, published in 2015 established that these compounds, including cyclophosphamide, are a risk factor for pulmonary veno-occlusive disease. In experimental models, cyclophosphamide exposure leads to venous remodeling, which, in turn, leads to the development of pulmonary hypertension.[29] Pulmonary veno-occlusive disease is extremely rare, with an incidence of 0.1-0.2 cases per million per year, and difficult to be differentiated from PAH. The gold-standard for the diagnosis of PAH, as previously mentioned, is right heart catheterization.[28]

Challenges and perspectives

Although the role of the RV in the development of cardiovascular diseases has been increasingly recognized, the best diagnostic and therapeutical approach in cardio-oncology has been poorly defined. Important challenges need to be addressed, as listed in Chart 1, including: definition of RVD in the context of cardiotoxicity, selection of the most appropriate method for its correct diagnosis, prognostic impact of RVD (either alone or in conjunction with the LC), and identification of specific therapies to prevent, attenuate and even reverse RVD associated with cancer therapy-induced cardiotoxicity.

The development and availability of diagnostic tools, as the use of strain echocardiography and wider use of CMR, opens the way to a better assessment of the RV. Cardio-oncology and new multicentric studies must include them to promote the understanding of the real impact of the RV and the development of interventions in cardiovascular care of oncologic patients.

Author Contributions

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Chart 1 – Challenges related to right ventricular dysfunction (RVD) in the cancer patient

- The condition is poorly recognized, but highly prevalent and even prior to left ventricular dysfunction;
- Diagnosis: diagnostic methods (strain, cardiac magnetic resonance) should be validated;
- Prognostic impact: multicentric studies, to assess the role of the right ventricle alone;
- Detection, interventions, and follow-up: not defined yet

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Review Article

Critical Analysis and Applicability of Imaging Methods in Monitoring and Diagnosing Ventricular Dysfunction in Patients with Cancer

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Abstract

Cardio-oncology is a subspecialty of cardiology that has become necessary as a consequence of the favorable impact of cancer treatment, which increases patients' survival rates, but makes them more prone to the cardiovascular side effects of cancer therapies in the short and long term. The presence of predisposing factors such as pre-existing cardiovascular disease, cardiovascular risk factors, genetic predisposition, previous antineoplastic therapies, and increased patient age is associated with a higher risk of cardiotoxicity in cancer treatment and may aggravate its complications. The use of imaging methods is fundamental in the management and detection of complications in cancer treatment. Echocardiography is considered the standard method for assessing left ventricular function and should be used in all patients. Magnetic resonance imaging is the best alternative for evaluation in patients with other associated conditions, especially advanced coronary disease, and in cases where it is difficult to obtain adequate echocardiographic images. Nuclear medicine offers options for patients for whom the use of echocardiography and magnetic resonance imaging is limited and for patients whose clinical and laboratory assessments conflict. Judicious use of imaging techniques leads to better patient outcomes during cancer treatment.

Introduction

Cardio-oncology is a subspecialty of cardiology that has become necessary as a consequence of the favorable impact of cancer treatment, which increases patients' survival rates, but makes them more prone to the cardiovascular side effects of cancer therapies in the short and long term. The presence of predisposing factors such as pre-existing cardiovascular disease, cardiovascular risk factors, genetic predisposition, previous antineoplastic therapies, and increased patient age is associated with a higher risk of cardiotoxicity in cancer treatment and may aggravate its complications.[1-3] The new European Society of Cardiology guideline defines cancer therapy-related toxicity in different stages. The mildest form of involvement is identified by the presence of elevated cardiac biomarkers (such as cardiac troponin) and/or abnormalities in cardiac strain with preserved left ventricular ejection fraction (LVEF) in asymptomatic patients. Accordingly, it is possible to observe that, for the detection of abnormalities resulting from cancer treatment, it is necessary to continuously monitor symptoms, biomarkers, and changes in imaging tests. The correct understanding of the use of these methods and their applicability, advantages, disadvantages, and limitations is crucial for good outcomes in cancer treatment.[2,4,5]

Keywords

Heart Failure; Echocardiography; Computed Tomography; Magnetic Resonance; Scintigraphy; Cardiotoxicity

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General principles for using cardiovascular imaging methods in assessment of cardiotoxicity

There are fundamental points about the use of imaging methods in the assessment of cardiotoxicity. Firstly, clinical evaluation prior to the beginning of cancer treatment is important to identify and treat cardiovascular risk factors and pre-existing cardiovascular diseases. Based on this information, a strategy involving adequate prevention and monitoring of patients should be developed for early identification of potential complications of cancer treatment (Figure 1). In addition to monitoring complications during cancer treatment, a strategy should also be drawn up for long-term patient follow-up, as a significant number of complications may arise after an active phase of cancer treatment. The use of reproducible, easily accessible techniques that have expertise and local familiarity and that cause the least number of risks for the patient should be taken into account when defining which technique should be used in the follow-up of patients.[2,3,6]

Echocardiogram

Chemotherapy-related cardiotoxicity, despite the recent growing interest, was first described in 1967.[7] For analyzing patients who will begin treatment with potentially cardiotoxic drugs, an overvaluation of the ejection fraction as a criterion of chemotherapy-related cardiotoxicity has been observed. This leads to a loss of diagnostic accuracy, since, depending on the treatment performed, the target lesion is unique. Therefore, the first Brazilian position statement on the use of multimodal cardiovascular imaging considers cardiotoxicity as any injury

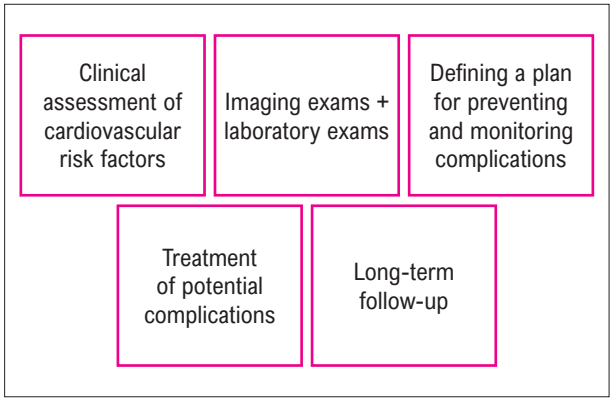

Figure 1 – *General principles for managing patients in cardio-oncology.*

to the cardiovascular system within a pathophysiological plausibility, which could range from pulmonary hypertension (desatinib), QT prolongation (arsenic trioxide), venous thrombosis (thalidomide), coronary disease (5-fluorouracil), myocarditis (checkpoint inhibitors), and others.[6]

The knowledge acquired in recent decades has allowed for changes in some important paradigms, including the classification of type I and type II cardiotoxicity. In the latter, the myocardial injury is said to be reversible (trastuzumab, for example), whereas, in the former, it is irreversible (anthracyclines). In 2010, Cardinale et al. demonstrated that, among patients with cardiotoxicity due to anthracyclines undergoing pharmacological intervention during the first 2 months, 64% had lesion reversibility.[8] Therefore, the aforementioned classification is in disuse. The first echocardiographic definition of chemotherapy-related cardiotoxicity in a clearer and more objective manner was proposed in 2014, described as an absolute drop in LVEF by 10 percentage points to values below 53%, assessed by the modified Simpson's biplane method, for example, a reduction of LVEF from 61% to 50%. Reassessment of LVEF after 2 to 3 weeks is recommended.[4] The rationale for recommending this reassessment is associated with two main points: a) the intrinsic temporal variability of the method, which can vary by up to 10 percentage points using the 2-dimensional technique;[5] b) the clinical conditions of patients with cancer, who usually present great variability of left ventricular (LV) preload and afterload, for example, dehydration, tachycardia, polypharmacy, anemia, infections, surgeries, diarrhea, vomiting, bleeding, exacerbated inflammatory response, etc. Accordingly, an attempt is made to minimize the effects of method variability. There is a concept that every systolic dysfunction presents associated diastolic dysfunction and that this precedes the reduced ejection fraction, mainly due to the pathophysiological model of the ischemia cascade. However, to the surprise of imaging specialists, the use of diastolic classification to assess cardiotoxicity according to the latest guideline of the American Society of Echocardiography remains controversial to this day, probably due to the clinical dynamics of these patients, in which there is constant lability of LV preload and afterload during treatment, as mentioned above.[9] Recently, in a cohort with breast cancer, it was demonstrated that a persistent change or worsening of diastolic dysfunction had little association with the subsequent risk of developing systolic dysfunction.[10] In 1998, the clinical application of myocardial strain analysis was demonstrated for the first time.[11] Only after the first decade of the 2000s, the first studies supported the use of LV global strain as a tool capable of diagnosing subclinical myocardial injury and predicting a drop in LVEF.[12,13] The CECCY Trial demonstrated that the use of beta-blockers to prevent cardiotoxicity was associated with an incidence of cardiotoxicity of 13.5% to 14.5%. Although carvedilol did not lead to a reduction in the early incidence of reduced LVEF, there was a significant reduction in troponin levels and in diastolic dysfunction.[14] On the other hand, in the first randomized, multicenter study evaluating the clinical impact of guiding therapy by 2-dimensional longitudinal strain in one arm and by the drop in ejection fraction using the 3-dimensional method in the other (SUCCOUR Trial), the patients who were treated in the strain arm had more pharmacological intervention and higher ejection fraction at the end of the study.[12]

In the Brazilian context of positions and guidelines, we have the Second Brazilian Guidelines on Cardio-oncology[6] and the First Brazilian Position Statement on the Use of Multimodal Imaging in Cardio-oncology.[2] Both documents agree on the criteria for follow-up during chemotherapy; they differ, however, on the cutoff point for subclinical cardiotoxicity. The guideline maintained the 15% relative drop in LV global longitudinal strain, while the position statement adopted a cutoff point of 12%, in line with the SUCCOUR Trial, given that it is the most robust study to evaluate the impact of drug intervention guided by the decrease in strain. The critical analysis of these documents is part of the burden of clinical individualization, which translates into cardio-oncology in more cardiotoxic chemotherapy treatment. In other words, if anthracyclines are being used, the image monitoring periods will be guided by that class of medication; if tyrosine kinase inhibitors are used, this class will guide monitoring. Until the publication of these 2 documents, echocardiogram was recommended before treatment and every 3 months in most classes of chemotherapy, with the exception of anthracyclines, with the subsequent echocardiograms at 2 months, 6 months, 1 year, and then annually. It may be performed earlier if the total dose of doxorubicin exceeds 240 mg/m^2, and it is recommended to repeat the echocardiogram at each 50 mg/m^2 increment in the total cumulative dose. Another situation where there is no clarity is monitoring during the use of checkpoint inhibitors. To date, no study has been able to demonstrate the role of echocardiography in predicting cardiotoxicity or myocarditis in this class. In this context, when facing suspicion, it is strongly recommended to perform cardiac resonance. Over the past years, another form of toxicity has been noticed, namely, the excess of imaging tests without clinical impact, especially in patients at a low risk for cardiotoxicity (young patients, no cardiovascular risk factors, low doses of anthracyclines, absence of radiotherapy). In 2022, the European Society of Cardiology published the update to its cardio-oncology guideline.[3] In this document, there is a change of perspective on monitoring patients with cancer who are exposed to chemotherapy. Instead of monitoring according

to the cardiotoxic agent, the recommendation is to monitor through clinical stratification using the HFA-ICOS score, which classifies the risks of cardiotoxicity as low, moderate, high, and very high. Only patients with high/very high risk should be referred to a cardiologist (class I) before starting treatment. Regarding systematic and serial echocardiograms, there has been a change in the performance of the exam, based on clinical stratification, with a baseline echocardiogram being recommended before the start of chemotherapy in all patients. However, serial performance throughout treatment will be guided by the patients' stratification according to the HFA-ICOS score. This rationale is extremely consistent from a clinical and cost-effectiveness point of view. On the other hand, the practicality of using it in daily clinical practice has become challenging, due to the uniqueness of each cancer treatment and each patient's risk stratification (Table 1). This European update has brought an interesting severity classification, considering the patient's functional status or the echocardiogram imaging data in asymptomatic patients.

This classification is important not only for prognostic stratification, but also for guiding therapy, which differentiates it from previous documents that did not categorize asymptomatic and symptomatic patients.

The incorporation of new technologies for monitoring cancer therapy-related cardiotoxicity, such as longitudinal global strain, allows for subclinical detection and more accurate monitoring during cardioprotective intervention (Figure 2).

Finally, although several studies have demonstrated that the assessment of LVEF by 3-dimensional echocardiography is quite robust, with values approaching the gold standard of cardiac volumetry (magnetic resonance imaging of the heart),[15] there is no demonstration of the superiority of monitoring cardiotoxicity using 3-dimensional LVEF in relation to the technique of LV global longitudinal strain.[16-18] Nevertheless, we must adopt a critical view of the subject, since cardio-oncology is a relatively recent science. In the other clinical scenarios, the assessment of LVEF using the 3-dimensional technique is a more accurate tool when available. Therefore, we must use as much information as we have available, always combining it with clinical rationale, seeking to improve the survival of these patients, mitigating risks and morbidities.

Table 1 – Cancer therapy-related cardiotoxicity

Symptomatic (HF)	Mild	Patient with mild symptoms, without worsening during cancer treatment
	Moderate	Outpatient requiring diuretic therapy and HF medication
	Severe	Hospitalized patient
	Very severe	Patient requiring inotropic agents or mechanical circulatory support; or under assessment for heart transplantation
Asymptomatic	Mild	Ejection fraction ≥ 50% and new relative drop by more than 15% in LV global longitudinal strain; and/or increase in myocardial injury biomarkers
	Moderate	New drop in ejection fraction to values between 40% and 49%, associated or not with elevated biomarkers and decreased LV global longitudinal strain
	Important	New drop in ejection fraction to values below 40%

HF: heart failure, LV: left ventricle; biomarkers: troponin. Adapted table.[3]

Nuclear cardiology

a) Radionuclide ventriculography in the monitoring of ventricular dysfunction

At the basis of cardio-oncology, the use of nuclear medicine has been one of the structuring forms of the ventricular function assessment protocol. Schwartz et al. used radionuclide ventriculography (often known as multigated acquisition or MUGA) to monitor patients treated with doxorubicin to detect small changes in LV function, in order to avoid elevated doses of doxorubicin and thus prevent significant cardiomyopathy.[19] In a pioneering manner, they demonstrated that the routine use of radionuclide ventriculography was associated with a reduced incidence of clinical heart failure to 2.8%, compared to 20.8% in patients receiving standard care without imaging.[19] Since then, the assessment of ventricular function has been routinely performed in patients treated with anthracyclines, and radionuclide ventriculography is now part of the assessment in a diverse range of patients. For its best use, it is necessary to understand its operational characteristics. The main advantages of radionuclide ventriculography are great intra- and inter-observer reproducibility, semi-automatic processing, widely available performance in nuclear medicine services, accuracy, little dependence on the operator, and the absence of contraindications related to renal dysfunction or allergy. The limitations to radionuclide ventriculography include the use of radiation (especially due to its repeated use) and the fact that the assessment of ventricular function is not accompanied by a structural analysis of the heart, the pericardium, the valves, or the state of the myocardium, as in magnetic resonance imaging.[1,20] It is important to emphasize the fact that the LVEF values obtained by echocardiogram are not consistent with those from radionuclide ventriculography. Some authors found that echocardiogram provides higher LVEF values than radionuclide ventriculography, which could lead echocardiogram to underestimate cardiotoxicity. It is very important to be aware of the specificities of imaging methods and be familiar with them for proper use.[21] In general, radionuclide ventriculography is best used in the following situations: when LVEF values on the echocardiogram are difficult to obtain (poor acoustic window); when LVEF values conflict with other results of clinical or laboratory tests or with clinical evaluation, as radionuclide ventriculography is more accurate and less dependent on operator proficiency; and when the LVEF value obtained by echocardiogram will lead to a significant change in the cancer treatment, such as interruption of a first-line cancer drug, in order to confirm the need for a change in strategy.[1,3,20,22]

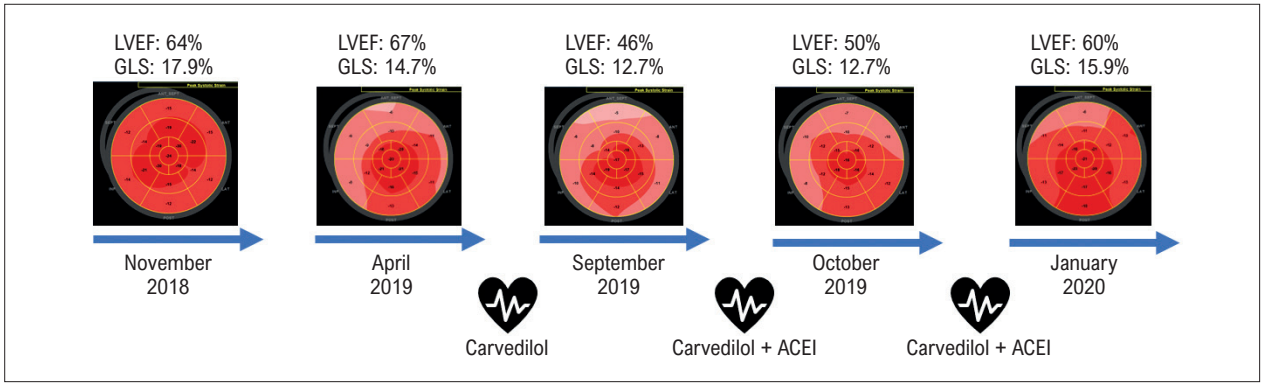

Figure 2 – *A 67-year-old patient with inoperable abdominal leiomyosarcoma who used docetaxel with gemcitabine as first line, then doxorubicin with dacarbazine, and currently using ifosfamide. In April 2019, she was asymptomatic, and a beta-blocker was prescribed due to subclinical cardiotoxicity (drop in global longitudinal strain greater than 15%), but the patient did not use the medication, returning 5 months later with heart failure and reduced ejection fraction. At that time, the patient was medicated with enalapril and carvedilol, evolving with clinical and echocardiographic improvement. ACEI: angiotensin-converting enzyme inhibitor; GLS: global longitudinal strain; LVEF: left ventricular ejection fraction.*

Figure 3 shows the example of a patient whose echocardiogram showed doubtful LVEF values making radionuclide ventriculography necessary to define management.

b) 123I-MIBG scintigraphy in the detection of cardiotoxicity

Changes in LV contractility function are relatively late in the cascade of damage secondary to cancer treatment. Earlier means of detecting cardiotoxicity have been proposed, such as the use of hyperstimulation of the adrenergic system, which is secondary to ventricular damage caused by antineoplastic agents. The tracer 123-iodine metaiodobenzylguanidine (MIBG) has demonstrated value in identifying patients with hyperstimulation of the adrenergic system and who are at increased risk of adverse events when suffering from heart failure with reduced LVEF.[23] An experimental study demonstrated that, after treatment with doxorubicin, cardiac 123I-MIBG uptake was significantly reduced 2 weeks later, followed by a decrease in LV end-diastolic volume and increased 18F-FDG uptake at 4 weeks, and, finally, by an increase in LV end-systolic volume and a decrease in LVEF at 6 weeks. Imaging of cardiac innervation is, thus, the earliest marker of anthracycline cardiotoxicity.[24] In Brazil, Guimarães et al. demonstrated that, in women with breast cancer undergoing chemotherapy, the evaluation of cardiac sympathetic activity with 123I-MIBG was an early marker of cardiotoxicity.[25] These data were recently reinforced by a systematic review with 12 studies using 123I-MIBG that indicated the value of the technique as an earlier method than echocardiogram in detecting cardiotoxicity; however, due to the methodological variability of the studies, further studies are recommended to confirm these findings.[26]

c) 18F-FDG PET CT in the assessment of cardiotoxicity

Increased myocardial uptake of 18-fluorine fluorodeoxyglucose (18F-FDG) appears to be a marker of early myocardial damage in cancer therapy. Experimental studies using radiotherapy in the cardiac area have shown that high uptake of FDG in an irradiated field appears to be related to myocardial damage in the microcirculation associated with mitochondrial damage.[27] Positron emission tomography (PET) with 18F-FDG is mentioned in the cardio-oncology position statement of the Brazilian Society of Cardiology as a means of diagnosing cardiotoxicity induced by immune checkpoint inhibitors, since it makes it possible to detect, evaluate the extent, and even quantify the inflammatory process of multiple cardiovascular conditions, such as myocarditis, pericarditis, and vasculitis.[28] Figure 4 displays how the main applications of nuclear medicine in cancer-related cardiotoxicity have expanded beyond the assessment of LV function.[29]

Cardiac magnetic resonance imaging

The improvement of cardiac magnetic resonance imaging techniques and the increasingly available access have expanded the role of cardiac magnetic resonance imaging into cardio-oncology. Recently, myocardial strain imaging and native T1 and T2 mapping have offered information beyond the quantification of ejection fraction, improving early detection of cardiotoxicity and predicting cardiac dysfunction without the use of contrast and radiation exposure.

Echocardiography is the first-line approach in the initial assessment of cardiac function, in the risk stratification of pre-existing cardiovascular disease, and in the imaging surveillance of cardiotoxicity during cancer treatment.[3,6] In some situations, echocardiographic evaluation is a challenge, for instance, in patients undergoing treatment for breast cancer who have breast implants, or in patients who have already undergone pulmonary lobectomy due to lung cancer with consequent displacement of the heart (Figure 5), making echocardiographic assessment difficult or even impossible.

In patients with a limited echocardiographic window or with doubtful echocardiographic findings, cardiac magnetic resonance imaging is recommended, and it is able to add important information to stress imaging in the risk stratification of coronary disease and in the suspicion of acute myocarditis related to cardiotoxicity.[3]

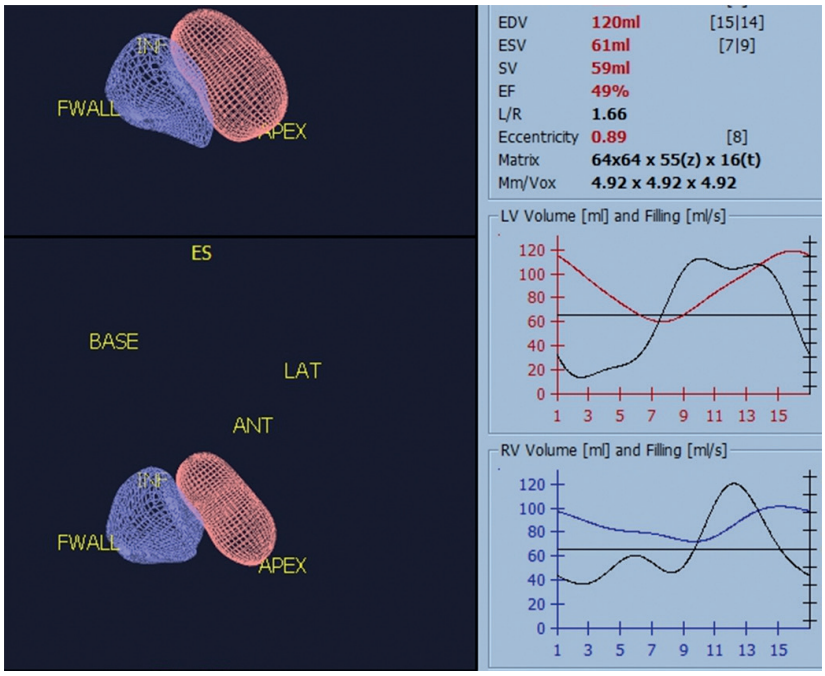

Figure 3 – *A 52-year-old patient undergoing treatment for breast cancer with doxorubicin and trastuzumab. After the second cycle, the echocardiogram showed a worsening of the left ventricular ejection fraction from 67% to 45%. Radionuclide ventriculography confirmed that left ventricular ejection fraction had dropped to less than 50% (49%), leading to temporary suspension of trastuzumab.*

a) Magnetic resonance imaging in the detection of early myocardial damage

Waiting for LVEF to drop during cancer treatment may imply irreversible cardiovascular damage and it may be too late for protective measures. The alteration of regional myocardial deformation occurs before myocardial dysfunction in these patients.[2,3]

Accordingly, the use of myocardial strain by cardiac magnetic resonance imaging has shown to be an effective tool not only in the early detection of cardiotoxicity, before the reduction of the ejection fraction, but also a tool capable of identifying patients at risk of developing cardiotoxicity and those with chances of recovery after established cardiotoxicity.

In a longitudinal study of cardiac magnetic resonance imaging, Giusca et al. used fast strain encoded magnetic resonance (fast-SENC) to demonstrate that the percentage of normal myocardium, defined as the number of segments with circumferential and longitudinal strain ≤ −17% divided by 37 (total of segments considered), between 60% and 80% identified patients at risk of developing clinical or subclinical cardiotoxicity, and that early cardioprotective therapies assist in ventricular recovery. On the other hand, patients with a percentage of normal myocardium ≤ 55% had a high risk of cardiotoxicity and a low chance of recovery.[18]

Myocardial deformation by cardiac magnetic resonance imaging can also be calculated using post-processing software (feature tracking) from cine images acquired in the standard protocol, even if the specific sequence of myocardial strain has not been performed. Nevertheless, cine images have lower spatial and temporal resolution for strain calculation by feature tracking than echocardiography using speckle tracking.[13]

b) Magnetic resonance imaging in cardiotoxicity monitoring

The risk of cardiovascular toxicity should be assessed in all patients before initiating cancer treatment to identify individuals with pre-existing cardiovascular disease or multiple risk factors, thus considering prevention strategies, guiding appropriate cancer treatment in high-risk patients, and ultimately mitigating the risk of myocardial injury and heart failure.[1]

The risk of coronary artery disease should be assessed by conventional risk scores, and cardiac magnetic resonance imaging is a good option for cardiovascular stratification with stress perfusion imaging and delayed gadolinium enhancement. Furthermore, cardiac magnetic resonance imaging is the gold standard for measuring left and right ventricular ejection fraction, volumes, and mass. Its ability to detect small changes with low operator dependence may represent early changes in treatment strategy and the initiation of protective measures, thus reducing myocardial injury.[30]

Recent data about damage to the right ventricle related to anticancer therapy have also shown the involvement of this chamber, similar to what occurs with the LV. Corroborating these findings, Souza et al. found a decrease in the right ventricular ejection fraction, an increase in diffuse interstitial

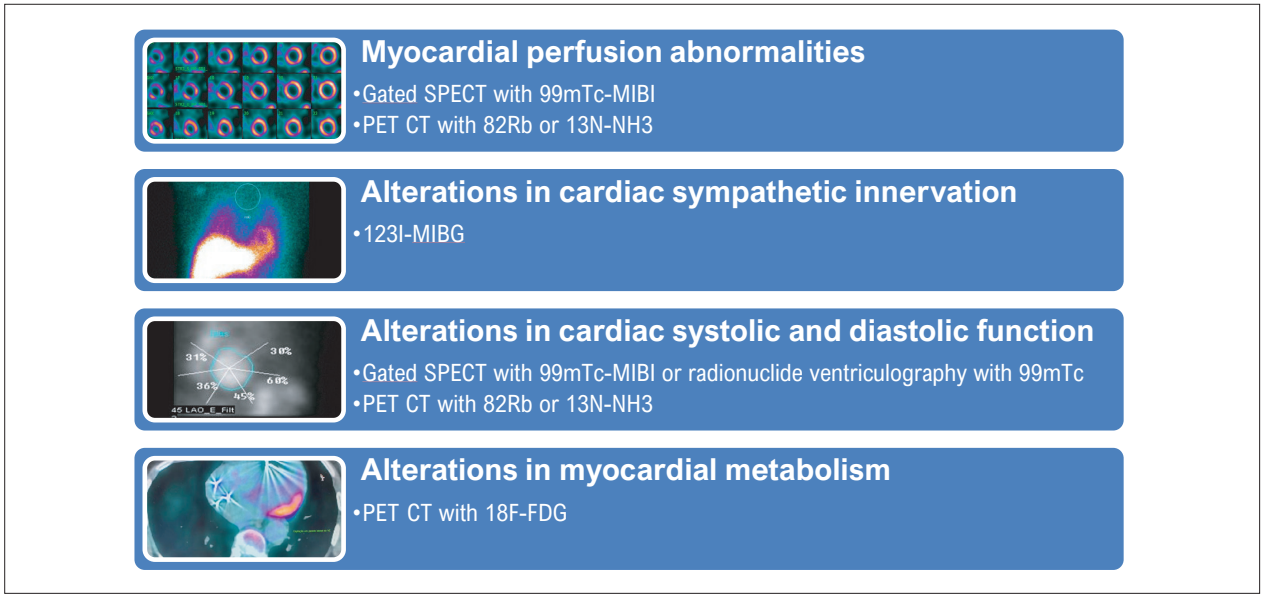

Figure 4 – *Main applications of nuclear medicine in the detection and monitoring of cancer therapy-related cardiotoxicity. 23I-MIBG: 123-iodine metaiodobenzylguanidine; 18F-FDG: 18-fluorine fluorodeoxyglucose; MIBI: sestamibi; NH3: ammonia; PET CT: positron emission tomography coupled with computed tomography; Rb: rubidium; SPECT: single-photon emission computed tomography; Tc: technetium. Adopted from Mesquita et al.*[29]

fibrosis, and a decrease in myocardial mass in 27 women undergoing treatment for breast cancer with anthracyclines, changes similar to those found in the LV.[31]

Conventional sequences of cardiac magnetic resonance imaging during the monitoring of patients undergoing cancer treatment add important information associated with cardiotoxicity or cancer-related complications. Acute pericarditis secondary to chemotherapy or mediastinal radiotherapy, or even involvement of the pericardium due to infiltration or metastatic spread, can be diagnosed with the combination of anatomical dark blood sequences, delayed enhancement, and cine imaging. Real-time cine sequences with free breathing and tagging provide additional information in cases of evolution to constrictive pericarditis.[32]

Although rare, immune checkpoint inhibitor-related myocarditis may be increasingly present in clinical practice due to the increasing use of immunotherapy in the treatment of cancer, and cardiac magnetic resonance imaging is particularly important in this scenario, as it is a non-invasive and accurate diagnostic tool. Parametric maps, although not included in the Lake Louise criteria,[33] when incorporated, have shown an evident gain in diagnostic accuracy, especially in the context of immune checkpoint inhibitor-related myocarditis.[34]

c) New magnetic resonance techniques for detecting cardiotoxicity

Tissue characterization by cardiac magnetic resonance imaging is a promising tool for early identification of cardiotoxicity. Consistent data have shown that edema, inflammation, and extracellular volume expansion occur before myocardial dysfunction in these patients.[30] Increased signal intensity in the myocardium on T2-weighted sequences reveals areas with increased water content that represent myocardial edema. Nonetheless, conventional imaging has some important limitations related to motion artifacts and bright subendocardial rims due to stagnant blood. In contrast, myocardial T2 mapping does not have these limitations and improves edema detection. Some studies have proposed the use of T2 mapping to identify myocardial edema as the first alteration caused by damage to the myocardium related to cardiotoxicity.

Galan-Arriola et al. correlated histopathological findings of doxorubicin-induced myocardial injury with T1 and T2 mapping, quantification of extracellular volume, and LVEF in an animal model. Cardiac magnetic resonance imaging was performed weekly before, during, and after anthracycline treatment, and T2 mapping showed changes prior to T1 mapping, extracellular volume, and LVEF. The histological correlation detected intracardiomyocyte edema without any other evident alteration in the structure of the myocardial tissue, and after suspension of the anthracycline there was no development of clinical or histological alterations.[35]

However, studies in humans have failed to demonstrate the significant role of T2 values in the context of cardiotoxicity. Tahir et al. studied changes in T1 and T2 mapping and myocardial strain in humans in the early detection of cardiotoxicity and found that T1 mapping was better able to detect cardiotoxicity than T2 mapping. The authors believe that this difference is due to the fact that they performed the control cardiac magnetic resonance imaging later and less frequently than Galan-Arriola et al. Therefore, T2 would be smaller or already normalized, while T1 would still be high.[35] This could explain why T1 mapping has a stronger data correlation with cardiotoxicity than T2 mapping.

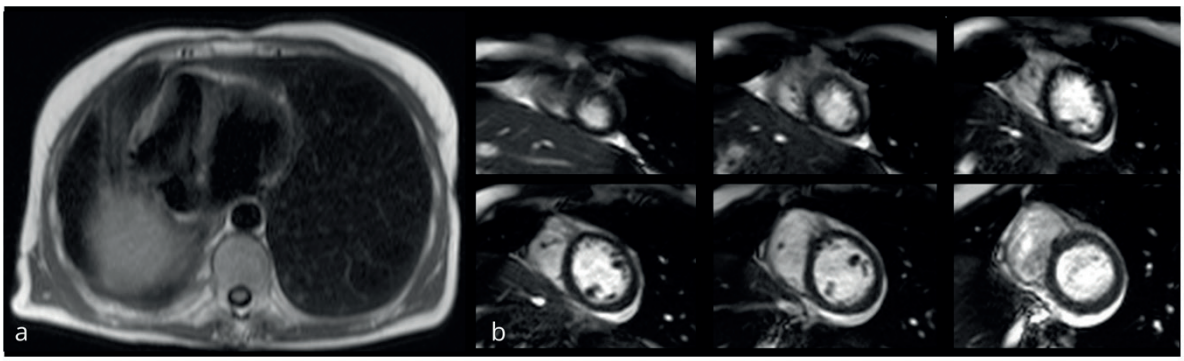

Figure 5 – *A 62-year-old woman with a history of right lower lobectomy due to lung cancer presenting with cardiac arrhythmias. The accentuated displacement of the heart to the right hemithorax seen by locating the chest axial sequence (in a) made echocardiographic evaluation impossible, but there was no limitation to evaluation by cardiac magnetic resonance imaging. In b, cine imaging of the short axis of the heart.*

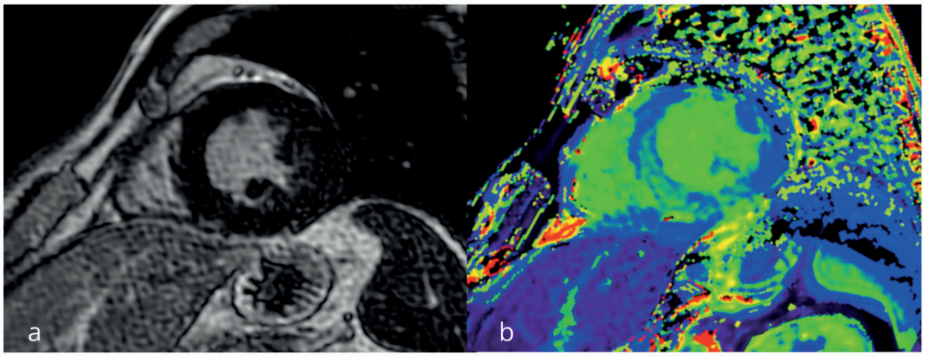

Figure 6 – *Delayed enhancement image without evidence of myocardial fibrosis (in a), but with increased native T1 (in b), in a 53-year-old man undergoing treatment for Hodgkin's lymphoma with doxorubicin, bleomycin, vinblastine, and dacarbazine, in addition to radiotherapy.*

Native T1 sequence identifies focal and/or diffuse myocardial lesion, without the use of contrast, before it can be detected by late gadolinium enhancement.[36] In addition, post-contrast T1 mapping offers the added benefit of quantifying extracellular volume already validated for fibrosis measurement. Considering the diffuse pattern of fibrosis most commonly found in this context, T1 mapping and calculation of extracellular volume are better predictors of the presence of fibrosis than delayed enhancement, seeing that focal fibrosis was detected by delayed enhancement in only 6% of patients treated with anthracycline-based chemotherapy (Figure 6).[37]

Multiple studies have demonstrated the potential of myocardial T1 and T2 mapping and calculation of extracellular volume in the early detection of cardiotoxicity.[18,30,34,36,37] However, the great heterogeneity between acquisition sequences, varying even between manufacturers, limit their use in clinical practice, especially in longitudinal comparison of patients. For patients in monitoring for cardiotoxicity, always performing follow-up with the same type of sequence and respecting the same acquisition parameters can mitigate these limitations.[38]

Conclusion

The care of patients with cancer has evolved substantially in the past decades with the majority of patients surviving the initial treatment. The management of patients with cancer involves planning strategies to monitor the potential complications of this treatment, especially in patients who already have cardiovascular risk factors or manifest cardiovascular diseases. Many cancer treatment survivors will experience various problems related to cancer and the treatment thereof, as well as late effects throughout their lives. Therefore, it is crucial to use reliable techniques to monitor ventricular function for successful treatment, thus ensuring adequate life expectancy and quality of life.

Author Contributions

Conception and design of the research; Writing of the manuscript and Critical revision of the manuscript for important intellectual content: Mesquita CT, Melo MDT, Leal ABP, Almeida ALC.

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Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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Review Article

Advanced Heart Failure in the Cancer Patient

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Introduction

Innovations in anti-neoplastic treatments have amplified the number of long-term survivors. Even with novel malignancy therapies, anthracyclines are the foundation of cancer treatment, especially in hematologic malignancies, sarcomas, and breast cancer.[1]

Heart failure (HF) has been described in up to 10% of tumor survivors, and the progression to end-stage HF in 2% to 3%. According to estimations grounded on retrospective registry data, such as United Network for Organ Sharing (UNOS) or Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) registries, 0.5-2.5% of patients undergoing advanced HF therapies such as left ventricular assist devices (LVAD) and orthotopic heart transplantation have had previous cancer treatment.[1]

These studies also revealed exceptional individualities of these patients with advanced HF. They are usually younger (44–53 years) and mostly women (62%–72%), and with less comorbidities. Despite the concern with the history of previous cancer and the sequelae of cancer treatment, many studies have suggested that these patients do not have worse outcomes than other cases of HF. Therefore, discussing advanced HF and its management in this population has become imperative.

Mechanical circulatory support in chemotherapy-induced cardiomyopathy

Patients with chemotherapy-induced cardiomyopathy (CCMP) and advanced HF are often precluded from heart transplantation because of the history of recently treated or current cancer. In these cases, mechanical circulatory support (MCS) may work as bridge to candidacy, destination therapy or even bridge to recovery of the patients.[1] Data are limited regarding MCS in CCMP.

Analysis of the INTERMACS including 3812 patients between June 2006 and March 2011 compared 75 patients (2% of total) with chemotherapy-induced CCMP in MCS with 1345 ischemic cardiomyopathy (ICMP) patients and 2392 non-ischemic cardiomyopathy patients (NICMP).[2] Patients with CCMP were younger, mostly women (72%) and with less comorbidities, and destination therapy was more common as an implantation strategy compared to the other two groups (33% versus 14% in non-ischemic and 22% in ischemic cardiomyopathy). There was no difference in INTERMACS profile or functional class, and left ventricular ejection fraction was similar between groups. Concomitant surgery (usually valve procedure) was more common in CCMP. Overall survival was similar between groups, and heart transplantation was possible for 29% of CCMP group, 32% of ICMP group and 36% of NICP group.

However, biventricular involvement is common in CCMP,[3] and in this publication,[2] surrogate markers of right ventricular dysfunction were more frequent in CCMP patients compared to the other two groups: CCMP patients had higher atrial pressure, lower pulmonary systolic pressure, and higher central venous pressure/pulmonary wedge pressure ratio. These findings were translated in a 19% rate of need for right ventricular mechanical support in CCMP, compared to 11% in NICMP and 6% in ICMP (p=0.006). The need for right ventricular mechanical support was associated with worse survival, while CCMP patients on LVAD had similar survival compared to the other two groups.[2]

In the analysis of INTERMACS registry, left ventricular recovery was present in only one patient in the group of CCMP. There are few case reports in literature of patients on LVAD or biventricular support in which MCS weaning was successful. A case report and literature review published in 2018[4] presents a case of biventricular support in a female patient with anthracycline-induced cardiomyopathy who was on a LVAD and had right ventricular assistance with a centrifugal pump and a membrane oxygenator. After 64 days, she was submitted to a mitral annuloplasty and was weaned from biventricular support eight days after the procedure. Other eight cases of LVAD support in CCMP patients were reviewed[4] and the time on support before weaning MCS varied from two to 17 months, suggesting recovery do not happen in the short term and long term MCS may be needed to enable recovery in this group of patients.

Myocarditis leading to cardiogenic shock may also be a consequence of cancer therapy.[5] The use of the antimetabolite 5-fluoracil or high doses of cyclophosphamide may rarely lead to myocarditis, but more recently the use of immune checkpoint inhibitors (ICI) has been associated with fulminant myocarditis in up to 1% of cases, with high fatality rate of 50%.[6] In

Keywords

Chemotherapy-induced Cardiomyopathy; Advanced Heart Failure: Ventricular Assist Devices; Heart Transplantation.

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ICI-related myocarditis, myocardium is infiltrated by T-lymphocytes and macrophages leading to myocyte death and acute cardiac dysfunction. Short-term MCS may be necessary in acute HF patients presenting cardiogenic shock, while immunosuppressive therapy with intravenous methylprednisolone is warranted. There are only case reports about MCS in this scenario,[7] and usual acute HF management is recommended by current guidelines in these cases.[8]

Heart transplant

Heart transplant (HTx) is an effective treatment for patients with advanced HF and may be considered in patients with cancer therapeutics-related cardiac dysfunction.[9] Due to the potential risk of relapse of primary neoplasia, resulting in lower long-term survival, malignancy within five years was previously considered a contraindication to HTx. However, data from large registries did not confirm this hypothesis.

In an analysis of the International Society for Heart and Lung Transplantation (ISHLT) registry of patients submitted to HTx between 2000 and 2008, 232 patients with chemotherapy-related cardiomyopathy were identified.[10] The most common malignancies were leukemia or lymphoma (33%) and breast cancer (31%). Short-term and long-term survival rates were similar to those with other cardiomyopathies. Allograft rejection in the first year after transplant was significantly lower and hospitalizations for post-transplant infections were higher in patients with chemotherapy-related cardiomyopathy. Those findings may be explained by persistent immunosuppression from previous cancer therapies. Skin cancer, but not malignancy recurrence or death from cancer, was more frequent. Only one case of cancer recurrence was seen, suggesting that this is not a big concern in selected patients with CCMP.

Similar results were found in an analysis of the UNOS registry comparing 453 HTx recipients with CCMP to 51,312 recipients with other causes of cardiomyopathy, between 1987 and 2011. Patients with CCMP were younger and more likely female. There was no significant difference in unadjusted 10-year survival or death due to malignancy rates between the groups. Actually, after adjusting for age, gender, and history of malignancy, the 10-year survival was even higher in the chemotherapy-related cardiomyopathy group.[11]

A more recent analysis of the UNOS registry was performed including patients listed for HTx from 2008 to 2018. This cohort included 18,270 patients (357 with CCMP, 10,662 with dilated cardiomyopathy and 7,251 with ischemic cardiomyopathy). Patients with chemotherapy-related cardiomyopathy were younger, predominantly women, less likely to be diabetic or to have an LVAD at the time of HTx. Breast cancer and hematologic malignancies were the most common type of neoplasia (44% and 25%, respectively). Short-term and long-term survival post-HTx were similar between the groups.[12]

Nevertheless, patients with restrictive CCMP and specially radiation seem to have worse prognosis. In another study using data collected between 2000 and 2015 from the UNOS registry, 87 patients with radiation-induced restrictive CMP were compared with patients with restrictive CMPs of other etiologies (n=1,049) and all the others (n=44,805). Patients with radiation-induced restrictive CMP were younger and more likely to have previous cardiac surgeries. They had longer lengths of stay after transplant and higher early and long-term mortality.[13]

Current guidelines suggest collaboration with oncology specialists to stratify patients according to their risk of tumor recurrence and no arbitrary observation time is recommended.[14] HTx should be considered when tumor recurrence is low based on tumor type, response to therapy, and negative metastatic workup.

Conclusion

The management of patients with advanced HF due to CCMP is highly controversial, both because there are few studies in this population and because of issues about the underlying disease and sequelae of its treatment. This concern is justified, since, as we discussed, this population has some peculiarities that affect treatment response. Although the overall outcome of patients with CCMP is not inferior to that of other etiologies, these patients may have worse prognostic factors, such as biventricular dysfunction, pulmonary hypertension, among others. In addition, concerns about cancer and its treatment often impact the decision for heart transplantation, although more recent studies have shown a similar progression to other cardiomyopathies. Therefore, better understanding the peculiarities of this population is important and justifies the advances in cardio-oncology in recent years, especially in the field of advanced HF.

Author Contributions

Conception and design of the research: Ferreira SMA, Belfort DSP; Writing of the manuscript: Ferreira SMA, Belfort DSP, Freitas AKE; Critical revision of the manuscript for important intellectual content: Ferreira SMA, Seguro LFBC, Bacal F, Moura LZ.

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Review Article

Cardiovascular Rehabilitation in Patients with Cancer

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Abstract

Advances in cancer treatment have increased patient survival, as well as susceptibility to cardiovascular disease, not only due to the increase in risk factors but also as a result of the treatment itself.

Cardiotoxicity related to antineoplastic drugs is one of the most feared cardiovascular effects during or after chemotherapy treatment, and it is associated with unfavorable prognosis in cancer survivors. Moreover, it reduces physical capacity and quality of life. In this scenario, the multimodal model of cardio-oncological rehabilitation has become a fundamental strategy in patients with high cardiovascular risk or risk for the development of cardiotoxicity, as well as for those with already established heart disease.

In this article, we will address the role of cardiac rehabilitation in patients with cancer and its particularities.

Introduction

Early detection and assertive treatment have transformed cancer from a practically fatal disease to, in many cases, a chronic condition. Due to the progress in oncological treatment and increased survival, the time of exposure to cardiovascular risk factors has become longer, and with it the prevalence of cardiovascular diseases in patients with cancer has increased.[1]

Successful oncological treatment, in many cases, is only possible with the use of drugs with a high potential for cardiotoxicity.[2] Thus, in several types of cancer, it is not uncommon for the risk of cardiovascular death to exceed the risk of tumor recurrence.[3] In this context, Patnaik et al. reported that cardiovascular disease was the leading cause of death in elderly female breast cancer survivors without previously diagnosed cardiovascular disease.[4] In relation to incidence, the occurrence of cardiotoxicity varies between 5% and 30% in clinical series, and it is more frequent in a subgroup with the following known risk factors: extremes of age, previous ventricular dysfunction, arterial hypertension, diabetes, use of combined chemotherapy, and mediastinal radiotherapy.[5]

Considering that most cancers can currently be considered as chronic diseases and that physical training is known to be beneficial in the treatment of several cardiovascular diseases, during the last two decades, several researchers have focused on the subject of physical activity and cancer. These studies have culminated in the recommendation of physical training not only for prevention, but also as an adjuvant therapy for diagnosis of different types of cancer.[6-8] The objective of this article is to present cardio-oncology rehabilitation in the current context.

Pre-participation assessment

The initial cardiological assessment of patients undergoing cancer treatment who will be submitted to potentially cardiotoxic therapies should include careful anamnesis and physical examination, a 12-lead resting electrocardiogram, and assessment of left ventricular function by echocardiography.[7]

It is important to monitor signs and symptoms of heart failure (HF) during chemotherapy treatment, because, although it occurs rarely, early clinical manifestations of toxicity from oncological treatment can culminate in cases of fulminant acute myocarditis and/or severe arrhythmias. As toxicity can appear at any time after the use of chemotherapy drugs (up to several years after the end of treatment), constant surveillance of clinical manifestations of HF is fundamental, especially during the first year after chemotherapy.

Table 1 contains important information to take into account before starting physical activity in patients with cancer, such as clinical assessment, with the suggestion of performing pre-participation stress tests, assessment of peculiarities of the consequences of cancer treatment (absence of significant anemia or thrombocytopenia, absence of neutropenia), and factors intrinsic to cancer treatment (well-being, absence of nausea/vomiting, absence of active infections or metabolic diseases).

Keywords

Rehabilitation; Cancer; Physical activity.

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Table 1 – Complementary assessment of patients with cancer before participation in rehabilitation. Adapted from Gilchrist et al.[8]

Normal functional testing
Cardiopulmonary exercise testing
Resting blood pressure ≤160/90 mm Hg
Normal blood pressure response to exercise
Absence of ischemia
Absence of ventricular arrhythmias
Normal O_2 saturation
Absence of symptoms
6-minute walk test
Resting blood pressure ≤160/90 mm Hg
Laboratory tests
Absence of severe anemia (< 8.0 g/dL)
Absence of neutrophilia > 500 mm^3
Platelet count > 50,000/μL
Absence of symptoms
Nausea during exercise
Vomiting within the past 24 hours
Disorientation
Blurred vision
Complications associated with cancer
Acute infection
Acute metabolic disease
New lymphedema
Mental or physical alteration during exercise
Unhealed wound
Bone or brain metastasis
Self-monitoring skills
Understands exercise functions
Understands how to use the equipment

Roles of functional capacity and physical activity

Functional capacity is a strong predictor of mortality and cardiovascular events,[9] and it is used both for prognosis and for indicating therapeutic intervention in a broad range of cardiovascular and non-cardiovascular diseases. Observational studies have reported a reduction in the number of cardiovascular events in people who regularly perform aerobic physical activity.[10]

Patients with cancer have markedly reduced physical capacity in the early stages of the disease. A study carried out with women with breast cancer between 40 and 50 years of age showed an average reduction of 32% in physical capacity in relation to healthy controls, at different phases of treatment. The same study also showed that peak oxygen consumption (VO_2) can be an independent predictor of survival in metastatic disease.[11]

There is evidence that cancer treatment also has a negative effect on physical capacity, regardless of the presence of cardiotoxicity. A meta-analysis of 27 studies including women with breast cancer showed a 17% and 25% reduction in physical capacity before and after adjuvant therapy, respectively.[12]

One of the most concerning adverse effects of antineoplastic therapy is undoubtedly cardiotoxicity. The presence of systolic ventricular dysfunction results in a significant increase in mortality, in addition to worsening of quality of life.[13] In addition to cardiovascular changes, adjuvant treatment compromises other systems such as skeletal muscle, resulting in loss of lean mass and muscle function with a consequent impact on functional capacity.[14]

A retrospective study of childhood cancer survivors showed a positive correlation between increased anthracycline dose and reduced physical capacity. In that same study, in spite of higher levels of NT-proBNP, only diastolic dysfunction was found as a structural alteration.[15]

Radiotherapy and/or chemotherapy are associated with reduced physical capacity in patients with cancer. Figure 1 shows the main determinants of low physical capacity in patients with cancer.

It is known that exertion intolerance is one of the most striking characteristics of HF, and it is associated with worse physical capacity, quality of life, and prognosis.[16] Studies have already shown that reduced physical capacity in patients with HF occurs similarly in different etiologies, such as ischemic, idiopathic, or hypertensive;[17] however, studies in humans who have developed HF secondary to cancer treatment are still scarce in the literature.

Benefits of physical activity in patients with cancer

In patients with HF, controlled studies have also demonstrated a positive impact of physical activity as an additional therapeutic measure, with improved exertion tolerance.[18] A study published by Antunes-Correa et al., showed that the improvement in physical capacity after 4 months of physical training occurs in a similar manner in patients with HF, regardless of etiology. However, this study did not include patients with cardiotoxicity.[17]

In experimental studies, there is a suggestion that exercise before the use of anthracyclines or aerobic training before and during the infusion of anthracyclines could reduce the impact of cardiotoxicity. Hayward et al.[19] used a juvenile rat model to assess whether a training protocol would reduce the impact of anthracycline-induced cardiotoxicity. One group underwent aerobic training concomitantly with doxorubicin infusion, and the study concluded that aerobic training, concomitant with the beginning of doxorubicin infusion, reduced doxorubicin-induced cardiotoxicity, in comparison with the untrained rats. Another study by Parry et al. demonstrated that the therapeutic efficacy of doxorubicin was not affected in rats trained prior to treatment with anthracyclines, but there was a reduction in ventricular dysfunction in the group of trained rats.[20,21] Several other

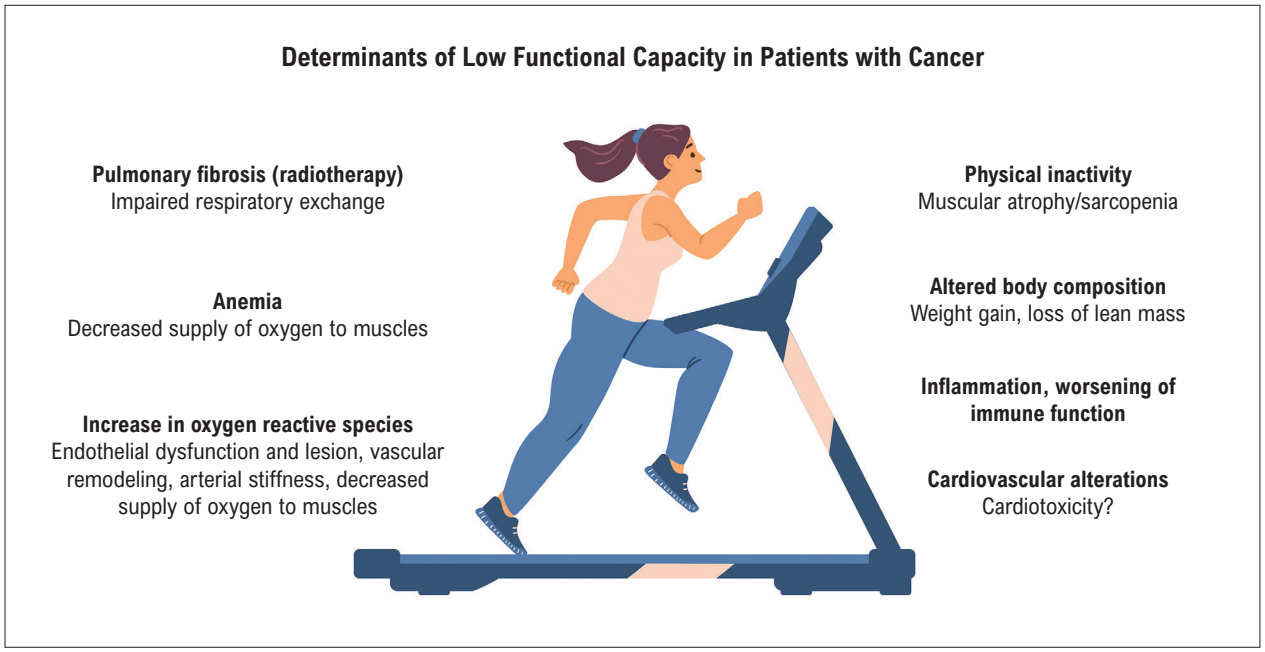

Figure 1 – *Determinants of Low Functional Capacity in Patients with Cancer.*

studies have also suggested a protective role for exercise both in acute toxicity of doxorubicin[22,23] and reducing the incidence of HF and ventricular dysfunction.[19,24,25]

In patients with cancer, several small randomized studies have demonstrated positive effects of exercise, such as an increased peak VO_2, improved vascular function, and improved LVEF (Figure 2).[8] Another, more robust study, with 4015 patients followed for 8 years, documented a reduced risk of events proportional to the performance of physical activity before the diagnosis of cancer; event-free survival was higher in patients who had previously practiced physical activity.[26] There is also a meta-analysis of more than 70,000 patients with cancer that demonstrated a strong association between functional capacity and prognosis, with a reduction in mortality in patients with better functional capacity over a 16-year follow-up.[27]

An important aspect of patients with cancer is that, in many cases, they face attacks by various agents, whether related to cardiovascular risk factors already present even before the diagnosis of cancer, the direct injury induced by cancer treatment, or indirect consequences of treatment such as sedentary lifestyle, weight gain, loss of muscle mass, among others.[28] Accordingly, exercise emerges as a therapeutic proposal to attenuate these multiple "hit points", given that it controls cardiovascular risk factors, improving the functional capacity of patients, reducing fatigue and improving quality of life.[28]

Components of rehabilitation in patients with cancer

The benefits of cardiovascular rehabilitation programs for non-oncological patients with cardiovascular comorbidities, such as coronary disease and HF are well established and are included as class I, level of evidence A recommendations, in all cardiology guidelines.

There is, thus, a considerable similarity in the assessment of patients with cancer in relation to the components and recommendations of prescription of physical activity. In both situations (cardiovascular and oncological rehabilitation), a multidisciplinary team is recommended, with prescription of aerobic physical activity and strength (resistance) exercises, in addition to education regarding the disease, treatment, psychosocial assessment, and lifestyle interventions, to optimize the control of cardiovascular risk factors (such as high blood pressure, diabetes, dyslipidemia, obesity, and smoking).[29] These components can be offered in rehabilitation centers with greater multidisciplinary supervision or as exercises performed outside the rehabilitation center, and it is highly recommended to individualize the prescription of physical activity and periodic reassessments to adjust the stimulus.[29] Figure 3 shows practical suggestions for implementing strategies for rehabilitation services and possible applications for monitoring patients who perform activities outside the rehabilitation center.[8]

However, in spite of similarities in these components, there are several particularities in advising patients with cancer. An example of this limitation regards the adverse effects of chemotherapy, and patients may experience fatigue, nausea, indisposition, loss of muscle mass, or postoperative convalescence, which are factors that do not correspond to the routine of cardiology patients.[30]

Table 2 contains data that summarize this comparison between cardiovascular rehabilitation and cardio-oncological rehabilitation, with several particularities related to patients with cancer.[6]

Regarding the objective prescription of intensity, frequency, and duration of aerobic and resistance exercises, there is no specific formal recommendation for patients

Setting	Clinical Outcomes	Cardiovascular Outcomes
Adjuvant		
Breast	↓ CVD Events ↓ CAD Mortality	↑ ↔ ↓ CRF ↓ LVEF
Prostate		↑ CRF
Colorectal		↑ CRF
Mixed (Meta-analysis)		↑ CRF
Post-adjuvant		
Breast	↓ CVD events ↓ All-cause mortality	↔ ↑ CRF ↑ Vascular function
Prostate		↑ CRF ↑ Vascular function ↔ Lipide profile ↔ Blood pressure
ASCC	↓ CVD events ↓ All-cause mortality	
Testicular		↑ CRF ↑ Vascular function ↑ Framingham risk score
Colorectal	↓ All-cause mortality	↑ ↔ CRF
Leukemia		↑ CRF
Lymphoma		↑ CRF
Mixe (Meta-analysis)		↑ CRF

Figure 2 – *Oncological scenarios studied with physical activity and observed outcomes. Even though they were small, there are multiple studies with various outcomes such as improved functional capacity, reduced mortality, improved vascular function, and improved left ventricular ejection.[8] ASCC: adult survivors of childhood cancer; CAD: coronary artery disease; CRF: cardiorespiratory fitness; CVD: cardiovascular disease; LVEF: left ventricular ejection fraction.*

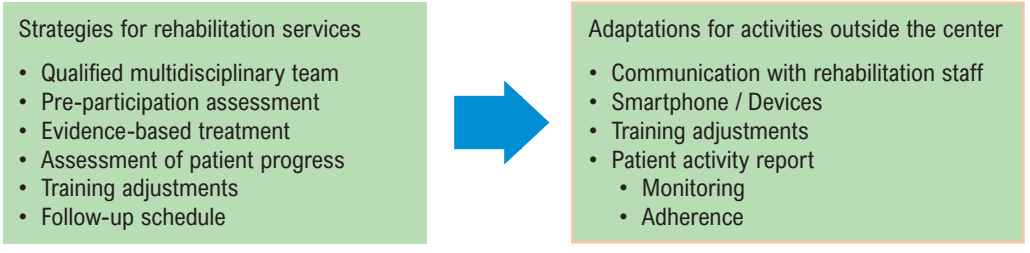

Figure 3 – *Strategies for rehabilitation services and solutions for monitoring patient adherence outside the rehabilitation center.[8]*

with cancer. Table 3 contains objective recommendations for exercise prescription based on guidelines for patients in cardiovascular rehabilitation, which may serve as parameters for prescription in this scenario.[29]

Conclusion

Rehabilitation is a multidisciplinary intervention with a great impact on improving functional capacity and quality of life and reducing cardiovascular outcomes. Patients with cancer, in addition to frequently having cardiovascular risk factors, undergo cancer therapy that can cause cardiotoxicity and culminate in a sedentary lifestyle with loss of muscle strength. Accordingly, with due attention to particularities in this patient profile, oncological rehabilitation should be encouraged and prescribed with the aim of complementing specific cancer therapy.

Author Contributions

Conception and design of the research: Schwartzmann PV, Gonzales A, Castro RRT; Acquisition of data:

Table 2 – Particularities of cardio-oncological rehabilitation in relation to cardiovascular rehabilitation. Adapted from Sase et al.[6]

Cardiac rehabilitation		Cardio-oncological rehabilitation
General conditions		Type of cancer, stage, metastasis
		Health conditions
		Treatment-associated cardiovascular alterations
		Lymphoma, ostomies, infection
		Blood count (cell count)
		Depression, fatigue, quality of life
		Functional capacity
Lifestyle modifications	Nutrition	Cancer-specific nutritional assessment
	Weight control	Body composition (gain or loss of fat mass)
	Blood pressure	Treatment of systemic arterial hypertension
	Lipid profile	Dyslipidemia control
	Diabetes mellitus	Glycemic control
	Smoking	Specific referral
	Psychosocial follow-up	Mental support
	Physical activity	Reduce sedentarism, increase physical activity
Prescription of physical exercise		Development of training guidelines, implementation of cardio-oncologic rehabilitation, strategies to improve outcomes in patients with cancer

Table 3 – Practical recommendations for prescribing aerobic and resistance exercises. Adapted from Bozkurt et al.[29]

	Aerobic exercise	Resistance exercise
Frequency	5 days/week, moderate intensity 3 days/week, high intensity	2 to 3 consecutive days/week
Intensity	Heart rate limit Vary intensity (interval)	Set load and repetitions. Goal of 8 to 10 exercises, 1 to 3 sets, 8 to 16 repetitions
Time	30 to 60 minutes, or less if high intensity	Varies according to capacity
Type	Any activity that raises heart rate, such as running, walking, cycling, or dancing	Resistance bands, dumbbells, machines, or own weight

Schwartzmann PV; Analysis and interpretation of the data and Writing of the manuscript: Schwartzmann PV, Gonzales A; Critical revision of the manuscript for important intellectual content: Gonzales A, Castro RRT.

Potential conflict of interest

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Review Article

CAR-T Cells Therapy: What Cardiovascular Adverse Effects Should We Expect?

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Abstract

Immunotherapy has emerged as a specific treatment, guided by oncologic targets, that has given the false impression (to oncologists and hematologists) that it had no adverse effects, including cardiovascular complications. Chimeric antigen receptor (CAR) T-cell therapy has certainly benefited specific patients; in contrast, reports of adverse cardiovascular effects have emerged. In this paper, we conducted a narrative review of conceptual aspects, clinical applicability, the cytokine release syndrome, extracardiac AE and, above all, the cardiovascular AE of CAR-T cell therapy. CAR-T cell therapy has been approved by regulatory agencies in the United States, Europe and Brazil, initially for the treatment of hematological malignancies at advanced stages, after failure or refractoriness. Among extracardiac AE, cytokine release syndrome and, consequently, encephalopathy, macrophage activation syndrome or hemophagocytic lymphohistiocytosis stand out. The most frequently described cardiovascular AE are cardiomyopathies, myocarditis and ventricular dysfunction; tachyarrhythmias, changes in QT and other electrocardiographic changes; pleural and pericardial disease, and changes in biomarkers. Thus, prior to the therapy, it is recommended to perform clinical evaluation, electrocardiogram, echocardiogram, and troponin and B-type natriuretic peptide measurements. The patient should be monitored during treatment with continuous electrocardiogram, serial echocardiogram, and biomarkers. Patients with severe cardiovascular AE should be admitted to a cardiac intensive care unit.

Introduction

Cancer treatment has evolved from surgery, radiotherapy and chemotherapy to a fourth and new pillar – immunotherapy.[1] Immunotherapy has emerged as a specific therapy, guided by oncologic targets, that has given the false impression (to oncologists and hematologists) that it had no adverse effects, including cardiovascular complications. However, with the use of this therapy, these effects not only occurred but were also found to be, in many cases, fatal. Another treatment modality, the chimeric antigen receptor (CAR) T-cell therapy, has undoubtedly benefited some patients. In other hand, case reports followed by cohort and pharmacovigilance studies have produced strong evidence of CAR-T cell therapy-induced cardiotoxicity. CART-cell is still an unknown topic for most cardiologists. Based on this, we conducted a brief, narrative review, of conceptual aspects, clinical applicability, cytokine release syndrome (CRS), extracardiac adverse effects, and above all, cardiovascular adverse effects related to CAR T-cell therapy.

Keywords

Immunotherapy, Adoptive; Receptors, Chimeric Antigen; Neoplasms

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CAR T-cell therapy

CAR-T cell: a new therapeutic modality

The immune system is an important tool in the fight against cancer, and several studies have demonstrated its activity even in pre-neoplastic stages. However, at diagnosis, the immune system activity is deficient or tolerant, allowing tumor expansion. In this context, the search for specific therapies that restore tumor control corresponds to the modern era of immunotherapy in onco-hematology.[2] Approximately ten years ago, a new antitumor therapy was successfully tested in childhood acute lymphoblastic leukemia (ALL), refractory to available therapies such as polychemotherapy and allogenic stem cell transplant. This new advanced cell therapy, developed by researchers from the University of Pennsylvania, consisted of collecting T cells from patients and changing of T cell receptors (TCR) by genetic engineering, to achieve high affinity and interact with specific targets expressed on the neoplastic cells, like CD19 present on B cells in ALL.[3] Following this laboratory stage, the patient was admitted to the hospital for pre-conditioning lymphodepletion, to receive a combination of immune suppressors, usually fludarabine and cyclophosphamide, and infusion of CAR-T cells. The patient was hospitalized from two to three weeks, during which the expansion and migration of CAR-T cells to tumor sites, as well as potential complications of the procedure occurred[4,5] (Figure 1).

Clinical applicability

Pivotal phase 2 studies have tested the principle and proved its efficacy and toxicity, with the cure of several cases

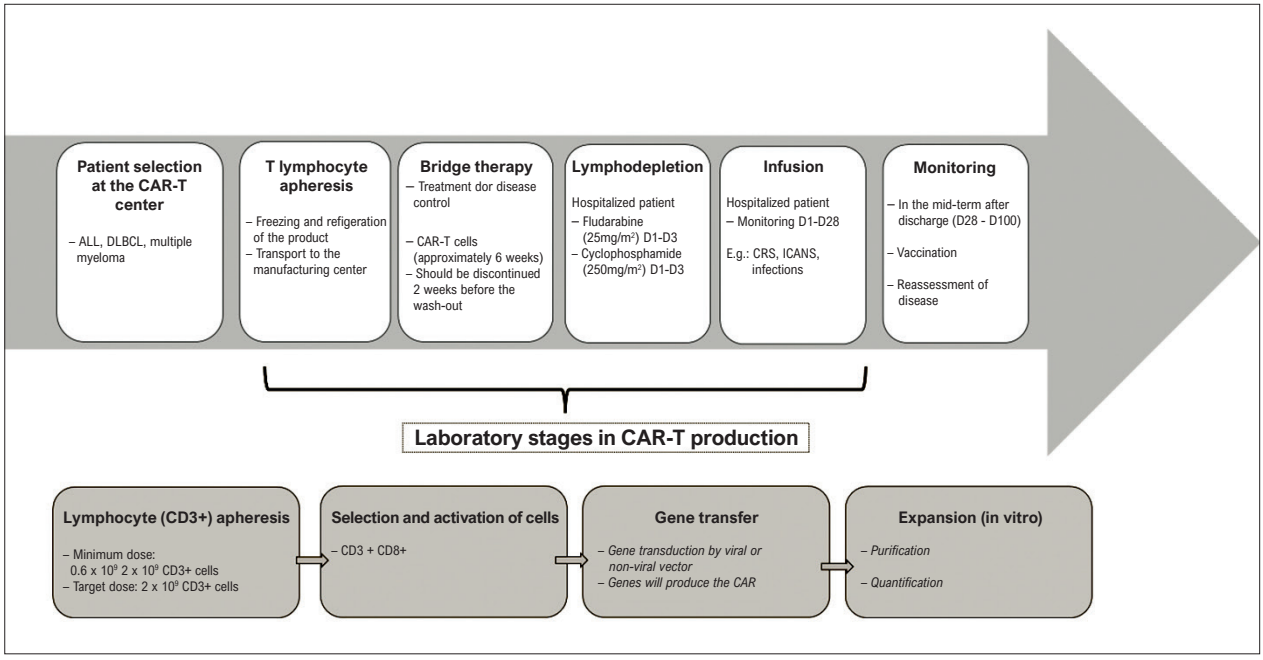

Figure 1 – *Stages of the chimeric antigen receptor (CAR) T-cell therapy. Adapted from Hartmannet al.,4 ALL: acute lymphoblastic leukemia; DLBCL: diffuse large B cell lymphoma; CRS: cytokine release syndrome; ICANS: immune effector cell-associated neurotoxicity syndrome; CAR: chimeric antigen receptor.*

of ALL and lymphomas, and control of relapsed and refractory multiple myeloma. A new therapeutic field has emerged, providing comfort and encouragement for patients with several incurable hematologic malignancies. An increasing amount of phase 2 and phase 3 studies have been testing strategies, molecules and therapeutic targets (Table 1).

Cytokine release syndrome (CRS)

The CAR-T cell therapy has specific adverse events (AEs) that should be early recognized and monitored during hospitalization, usually in bone marrow transplant units, and by a trained multidisciplinary team for the effective management of these complications. CRS is a common complication, affecting up to 90% of patients under treatment, and occurring from the first 24 hours to two weeks after the infusion. This syndrome is attributed to the increased release of inflammatory cytokines, such as interleukin-6 (IL-6), interferon-gamma (IFNγ), tumor necrosis factor alpha (TNF-α) and interleukin-1 (IL-1).[11] Risk factors for CRS include the type of disease treated, the manufactured CAR-T cell product, and the dose of CART cells. Due attention should be paid to fever, which is the first symptom of CRS and may appear already on the first day after infusion. Persistence of fever elevates the grade of this AE, and indicates immediate intervention with anti-interleukin 6 (tocilizumab). This drug is indicated to all patients with AE grade greater than 2, who then present, in addition to fever, hypotension of hypoxemia. For most patients who receive early treatment, AE will not progress to higher grades and subsequent clinical worsening and further need of vasopressors, mechanical ventilation or intensive care (Figure 2). Differential diagnoses of CRS include sepsis, tumor lysis syndrome, pulmonary thromboembolism and primary cardiac arrest or cardiogenic shock.[12]

In laboratory monitoring, it is also of great value to measure C-reactive protein and ferritin, which are increased in SLC, and fibrinogen, whose levels are low in SLC.[13]

Extracardiac adverse effects

In the spectrum of CRS-associated complications, a new type of encephalopathy has been reported, the immune effector cell-associated encephalopathy (ICANS). In the KarMMa[9] e Cartitude-1[10] studies, ICANS was developed in 18% and 16% of patients, and was of grade ≥ 3 in 4% and 2.1%, with median time to onset of two and eight days, respectively.[9,10] In general, ICANS occurs after CRS, and clinically presents as different signs and symptoms including delirium, encephalopathy, aphasia, lethargy, difficulty in concentrating, agitation, headache, shivering, convulsions, and rarely, cerebral edema. This syndrome is usually reversible, has its own grading system, and must be followed by neurologists during all steps of the procedure. One of the earliest symptoms may be agraphia, and because of that all patients are encouraged to write their names as a form of assessment. Neuroimaging tests, electrocardiogram, support measures, in addition to anticonvulsants and corticosteroids may be required in some cases.

Among the frequently reported AEs are persistent cytopenias, sometimes characterized as macrophage activation syndrome or hemophagocytic lymphohistiocytosis that can be treated with Anakynra (not available in Brazil). The risk of infections is multifactorial, and related to neutropenia, T cell depletion, and persistent

Table 1 – Pivotal studies on chimeric antigen receptor (CAR) T-cell therapy and cytokine release syndrome with clinical applicability

Clinical study/ Authors	Disease (*Relapsed or Refractory*)	CAR-T cell type	Target	CRS/n total (%)	CRS (%) *Grade 3-4*	Time of onset (median)
Juliet Schuster et al. [6]	Lymphoma*	Tisagenlecleucel Kymriah	CD19	64/111 (58)	22	3
Eliana Maude et al. [7]	ALL	Tisagenlecleucel Kymriah	CD19	58/75 (77)	25 *(43 ICU admissions)*	3 (1-22)
Zuma-1 Neelapu SS et al. [8]	Lymphoma*	Axicabtagene ciloleucel Yescarta	CD19	94/101 (93)	13	2 (1-12)
KarMMa Munshi NC et al. [9]	Multiple myeloma	Idecabtagene vicleucel# Abecma	Anti-BCMA	107/128 (84)	5	1 (1-10)
Cartitude-1 Berdeja JG et al. [10]	Multiple myeloma	Ciltacabtagene autoleucel Carvykti	Anti-BCMA	92/97 (95)	5.4	7 (1-12)

*# not approved in Brazil; CRS: cytokine release syndrome; ALL: acute lymphoblastic leukemia; * diffuse large B cell lymphoma; ICU: intensive care unit.*

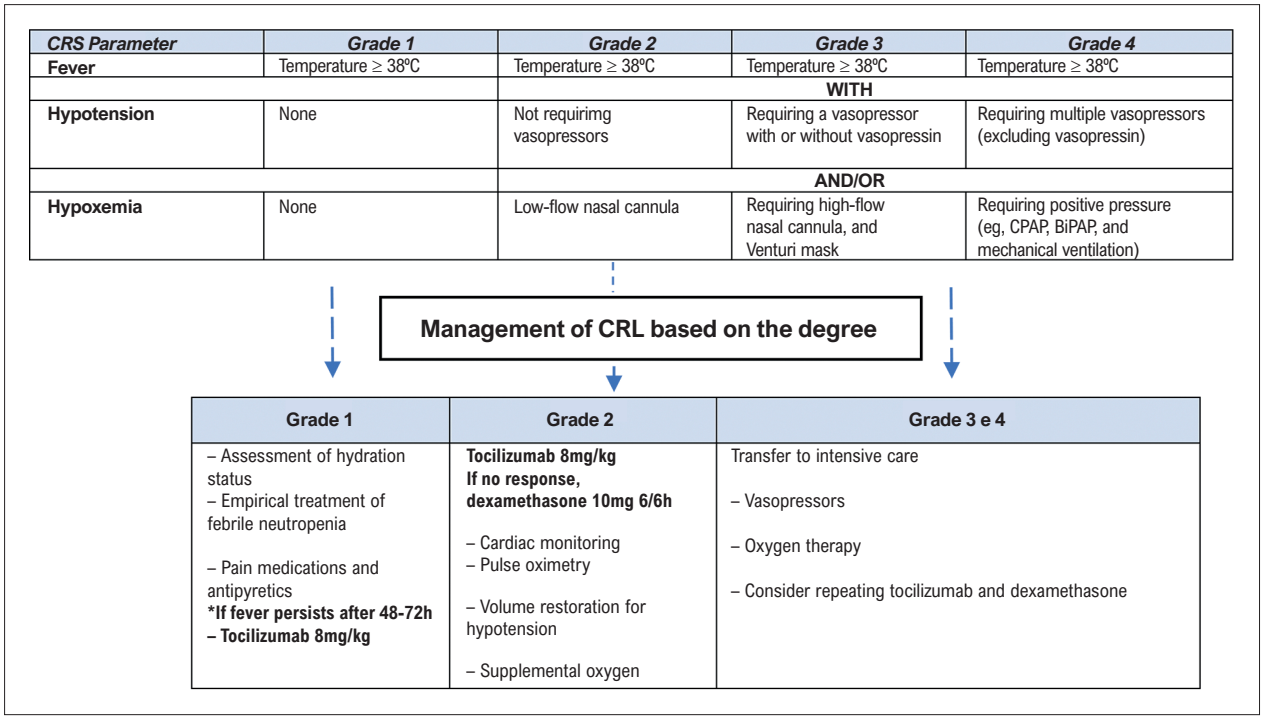

Figure 2 – *American Society for Transplantation and Cellular Therapy consensus on cytokine release syndrome grading and management. Adapted from Lee et al.,12 CRS: cytokine release syndrome.*

hypogammaglobulinemia.[10] All patients are vaccinated, starting three months after the procedure, including against SARS-CoV 19 and receive prophylaxis against *Pneumocitis carinii* with cotrimoxazol and against herpes simplex virus and herpes zoster with acyclovir. Patients with IgG <400mg/dL and those with repeated infections should receive intravenous immunoglobulin. Patient monitoring for viral infections such as cytomegalovirus, Epstein-Barr virus, HHV6 and adenovirus, and fungal infections with *Aspergilus* sp. and *Candida* sp. is recommended.[14]

Current scenario of CAR-T cells in Brazil and the world

The CAR-T cell therapy has been approved by regulatory agencies in the North America, Europe and in Brazil (by ANVISA), for the treatment of advanced hematological malignancies, after failure or refractory treatment. There are ongoing phase 3 studies in hematology on earlier stages of the disease and myeloid neoplasms, as well as researches on solid tumors and autoimmune disorders. Several strategies, tumor targets and allogeneic cart T-cells have been explored, to reduce the time between cell production and treatment. This new modality of advanced cell therapy has expanded

and been patented as a pharmaceutical industry product with specific manufacturing centers distributed over the world. In Brazil, the first experiences have been made in bone marrow transplant units of onco-hematology centers. The first case reported were patients from international clinical studies, and the first cases of patients covered by the supplementary health care have also been reported. In addition to its high complexity, an obstacle to the implementation of CAR-T cell therapy is its high cost. The solution to improve the access to the therapy in China, Spain and Canada has been initiatives for an autonomous production. In Brazil, the group from Hemocentro in the city of Ribeirao Preto, and the Butantan Institute in Sao Paulo have developed research with own manufacturing and history of successful infusions.[15]

Cardiovascular adverse effects of CAR-T cell therapy

CAR-T cell therapy is relatively new in oncology, and knowledge about adverse effects has been obtained primarily from case reports and subsequently from retrospective registry of patients at referral centers.

The cardiovascular adverse effects of CAR-T cells are not negligible. Lefrebve et al.[16] evaluated 145 adults undergoing CAR-T cell therapy and observed 41 (28.3%) events, including cardiovascular deaths, heart failure, acute coronary syndrome, ischemic stroke and new arrhythmias. The events occurred early, within a median of 11 days after the therapy was implemented. Elevated serum creatinine and CRS grades 3 and 4 were predictors of outcomes.

In 2019, Alvi et al.[17] studied 137 patients who received CAR-T cells in two hospitals in the USA. Troponin elevation was relatively frequent in patients with CRS who received CAR-T cells, who also had an increased risk for cardiovascular events subsequently. Patients with more severe CRS are at higher risk for severe adverse events.

Historically, cardiotoxicity has been associated with cardiomyopathy and heart failure. During CAR-T cell therapy, approximately 10% of patients develop cardiomyopathy, which was a level-2 predictor of CRS. The frequency of cardiomyopathy is higher among patients with cardiovascular risk factors. Nearly half of patients who develop ventricular dysfunction do not return to baseline function.[18] Adverse cardiovascular effects correlate not only with CRS but also with neurotoxicity.[19]

Data on larger number of patients come from the retrospective registry of pharmacovigilance of the adverse cardiopulmonary effects of the US Food and Drug Administration.[19-21] According to this registry,[21] of the 2,657 patients who received industrialized CAR-T cells, 546 (20.5%) had adverse effects, with an overlapping with CRS in 373 patients (38.3%). Lethality rate among patients who had cardiopulmonary adverse effects was 30.9%, and atrial fibrillation was the most common tachyarrhythmia reported. The main cardiovascular effects are listed in Table 2.

Some inferences can be drawn from these registries that are relevant from the perspective of clinical applicability: (a) to assess the risk of cardiotoxicity in candidates for CAR-T cell therapy; (b) to start the assessment with clinical history and physical examination; (c) to perform routine echocardiography to evaluate heart valve function and exclude valve diseases; (d) patients (candidates for the therapy) should have their cardiovascular status optimized by a cardiologist; (e) an early recognition and treatment of CRS reduces the risk of cardiotoxicity; (f) most cardiopulmonary adverse events have been reported in the first 30 days of treatment; and (g) patients who had received immune checkpoint inhibitor are at higher risk for CAR-T cell-associated cardiotoxicity.[21] The most commonly reported cardiovascular effects were severe arterial hypotension requiring inotropic support (4-33%); left ventricular systolic dysfunction (2-10%); pulmonary edema (4-6%); volumetric overload (5%); electrocardiographic changes; and biomarker changes, especially NT-ProBNP and troponin.[20]

Table 2 – Cardiovascular adverse effects secondary to chimeric antigen receptor T-cell therapy according to notifications to the US Food and Drug Administration

Cardiopulmonary adverse effect	n and frequency (n total= 2,657)	Risk rate and 95% confidence interval
Tachyarrhythmias	74 (2.8%)	2.21 – 3.51
Cardiomyopathies	69 (2.6%)	2.42 – 5.09
Pleural disease	46 (1.7%)	2.92 – 5.23
Pericardial disease	11 (0.4%)	1.25 – 4.09

Font: Goldman et al.[21]

Consensual recommendations

Although CAR-T cell is a new therapy, there are already recommendations issued by specialist societies. We will first mention clinical practice guideline on immune effector cell-related adverse events of the Society for Immunotherapy of Cancer (SITC).[1] The authors used the definition and nomenclature of cardiotoxicity established by the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE), and considered as cardiovascular adverse effects secondary to CAR-T cells the following: (a) new arterial hypotension; (b) decompensated heart failure; (c) heart failure combined with new arrhythmias such as atrial fibrillation or flutter; (d) nonsustained ventricular tachycardia; (e) prolonged QTc interval in the presence or absence of drugs that prolong the QT interval or electrolyte disturbances; (f) narrow or wide QRS complex tachycardias; (g) pericarditis; and (h) myocarditis.[1] Echocardiography is an accurate and accessible method for measuring ventricular function before the CAR-T cell therapy is started.

The SITC recommends:[1]

- Baseline cardiac assessment prior to CAR-T cell therapy by transthoracic echocardiogram, and troponin and N-terminal pro-brain natriuretic peptide (NT-proBNP) measurement;
- Troponin and LVEF should be monitored in patients who develop CRS of American Society for Transplantation and Cellular Therapy (ASTCT) grade ≥ 2;

- Patients with established and severe cardiovascular disease such as heart failure, previous myocardial infarction, and arrhythmias should be assessed and may be excluded from the CAR-T cell therapy;
- In evidence of cardiotoxicity, elevated troponin, decrease in LVEF or clinically significant arrhythmias, IL-6 blockade and/or steroids should be considered;
- Antiplatelet agents such as aspirin and clopidogrel should be discontinued prior to CAR-T cell therapy. However, high-risk patients who recently underwent a coronary revascularization, management decisions should be individualized, and made in conjunction with the cardiology team;
- Anticoagulants should be changed to short-acting agents. If platelet counts drop below 50,000/μL, all anticoagulants should be discontinued unless the patient has had a recent thrombosis. In these cases, the dose should be reduced, or platelet transfusions should be considered.

The European Society of Cardiology (ESC) recommends if clinical suspicion of cardiovascular complication:[22]

- Baseline electrocardiogram
- Continuous electrocardiographic monitoring
- Transthoracic echocardiogram
- Monitor cardiac troponin and B-type natriuretic peptide (BNP)
- Severe patients should be admitted to cardiac intensive care unit

Conclusions

Cardiovascular adverse events secondary to the CAR-T cell are frequent and severe, and justify the screening, monitoring, and early diagnosis and intervention to improve the outcomes of survival and quality of life. Data on this topic, obtained by careful work, are still lacking to answer specific questions.

Author Contributions

Conception and design of the research, Acquisition of data and Critical revision of the manuscript for important intellectual content: Martins WA, Magalhães Filho RJP, Galvão TFG; Analysis and interpretation of the data: Magalhães Filho RJP, Galvão TFG; Writing of the manuscript: Martins WA, Magalhães Filho RJP.

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Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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Viewpoint

Functional Capacity in Cardiotoxicity: Effects of Physical Exercise

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Abstract

Heart failure induced by chemotherapy is an adverse event of cancer treatment that results in high morbidity and mortality. Previous studies have shown that physical exercise improves functional capacity in patients with heart failure due to other etiologies. However, studies with a multimodal approach, including exercise interventions in patients with cardiotoxicity, are still scarce in the literature. The objective of this article was to discuss the effects of physical training in patients with heart failure induced by chemotherapy and the role of cardio-oncological rehabilitation as a tool to improve functional capacity and quality of life in this group of patients.

Introduction

The evolution that oncology has achieved in recent decades, both in diagnostic methods and therapeutic efficacy, has resulted in more cancer survivors. This has brought the later costs of successful oncological therapy to the surface, for example, treatment-induced cardiovascular toxicity. This situation is defined by early or late damage to the cardiovascular system, which originated during or after cancer treatment, as a result of antineoplastic therapies.[1] Although it does not occur in the majority of survivors, cardiotoxicity is the main cause of death associated with oncological treatment, especially in breast cancer survivors.[2] The complexity of cancer care and the management of multiple comorbidities presented by patients demonstrate that it is necessary for them to receive an integrated and multidisciplinary therapeutic approach.[3]

Cardiotoxicity can be caused both by classical chemotherapy treatment and by more modern strategies with radiotherapy, leading to various cardiovascular effects, such as arrhythmias, cardiomyopathy, endothelial dysfunction, and heart failure.[4] Different definitions have been proposed for cardiac dysfunction associated with cancer therapy. The most recent include, in addition to the severity of symptoms or altered echocardiographic parameters, such as reduced ventricular function, changes in global longitudinal strain or cardiac biomarkers.[5]

Keywords

Exercise; Cardiotoxicity; Cardiac Rehabilitation

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Chemotherapy agents such as anthracyclines have been significantly associated with an increase in the incidence of cardiotoxicity and its severe consequences, such as heart failure and cardiomyopathy.[6,7] Risk increases significantly depending on the dose used or the association with other drugs, such as trastuzumab.[8,9]

There effects are often clinically silent until their severity causes symptoms and requires treatment; the timeframe can range from days to years after chemotherapy. For anthracyclines alone, the negative effects on cardiac function can appear up to 20 years after treatment, whereas, in combination with trastuzumab, cardiac complications are earlier, and they may be present up to 2 months after their use, in 27% of patients.[10] A study of leukemia survivors treated with anthracyclines showed worsened left ventricular shortening fraction and contractility 12 years after diagnosis.[11]

Pharmacological and non-pharmacological strategies, such as ceasing smoking and alcoholism, control of cardiovascular risk factors, healthy diet, weight maintenance, and encouragement of aerobic physical exercise practice, have increasingly proven to be effective as cardioprotective measures.[12] Studies have shown that physical exercise is an effective tool to mitigate the effects of chemotherapy on the cardiovascular system.[13,14]

Early diagnosis and intervention can prevent progression to heart failure in patients with cardiotoxicity.

Although there is substantial evidence of the benefits of physical exercise before and during therapy with cardiotoxic drugs, there is a lack of studies that demonstrate the impact of exercise in adult patients with chemotherapy-related heart failure, and it is not clear whether these interventions can be performed with the same effectiveness as in other populations.

In this article, we seek to address the impact of physical training on patients with heart failure induced by chemotherapy and the role of cardio-oncological rehabilitation as a tool for improving functional capacity in this group of patients.

Impact of cardiotoxicity on functional capacity

The reduction in cardiorespiratory fitness in patients with cancer is multifactorial. The patients are usually less active, and they commonly have other complications secondary to the disease, such as pulmonary and musculoskeletal alterations. It is also necessary to consider that patients with cancer are generally older and are subject to the deleterious effects of aging itself. Reduced functional capacity can also be a consequence of the treatment itself.

Cancer patients show a reduction between 5% and 22% in physical capacity, regardless of the antineoplastic regimen used, even in the absence of cardiotoxicity.[15] A study that involved 248 women with breast cancer between 40 and

50 years of age, divided according to the treatment phase or presence of metastasis, showed an average reduction of 32% in functional capacity compared to healthy controls.[16]

A study on patients with esophageal cancer showed a significant reduction in cardiac function and physical capacity immediately after the end of chemoradiotherapy.[17]

Cumulative doses of anthracyclines also appear to impact exercise capacity, even in the absence of systolic dysfunction, as shown by a study of childhood cancer survivors.[18]

Effects of physical training

The result of a meta-analysis of 27 studies published by Scott et al. showed that physical training is an effective strategy to improve physical capacity in patients with early-stage cancer, in addition to being safe and feasible.[19]

Fatigue associated with cancer is a complaint frequently reported by patients, and evidence suggests that physical training promotes a significant reduction in symptoms.[20]

In a study published by Courneya et al., aerobic and resistance physical training significantly improved physical fitness, body composition, and chemotherapy completion rates in patients with breast cancer.[21] Other studies have shown that exercise also improves functional capacity, quality of life,[22,23] and possibly the survival of patients with cancer.[24]

In heart failure, it is known that functional capacity is markedly reduced, and studies have shown an improvement of 12% to 31% with physical training.[25]

Some randomized clinical trials have demonstrated potential improvement in cardiovascular health in non-oncology patients with heart failure through exercise rehabilitation,[26-28] and meta-analyses have shown positive effects on cardiac function and quality of life.[29-33]

The effects of exercise in patients undergoing chemotherapy have mainly been studied in terms of its cardioprotective role. In an observational study, Foulkes et al. investigated the role of exercise or usual care in the functional capacity and echocardiographic parameters of 28 women with breast cancer undergoing chemotherapy with anthracyclines, after 4 and 16 months of treatment. After 4 months of treatment, the group undergoing training showed a 6% reduction in peak oxygen consumption (VO_2) compared to the usual care, where this reduction was 18%. This reduction was maintained over 16 months. Despite small reductions observed in resting left ventricular ejection fraction, only 2 patients met the criteria for defining cardiotoxicity.[34] The mean reduction of 8% in physical capacity over the 16 months becomes even more relevant when we consider that the aging is typically associated with a reduction of 8% to 23% per decade.[35]

A single randomized study evaluated the impact of physical exercise on functional capacity in patients with chemotherapy-related cardiomyopathy. Participants were randomized to a control group or a group that received supervised training for 16 weeks. However, 78% of the patients selected for the supervised group did not accept to participate in the original design and received home training as an alternative. The exercise program consisted of 30 minutes of supervised exercise on a stationary bicycle, at an intensity of 50% of heart rate reserve, at a training frequency of 3 times/week for 16 weeks. The home program began with a supervised session, followed by prescription for maintenance of aerobic exercises such as walking, in addition to counting steps using a pedometer, for 16 weeks. Intensity was assessed using the Borg "6–20" rating of perceived exertion (RPE) scale at an RPE of 12. Outcomes included evaluation of functional capacity by peak VO_2, left ventricular ejection fraction, severity of heart failure symptoms using the MD Anderson Symptom Inventory for heart failure (MDASI-HF), quality of life using the Medical Outcomes Study 36-item Short-Form Health Survey (SF-36), and physical activity level in hours of exercise and intensity. Of the 16 participants randomized for training, only 10 completed the study, and 8 underwent functional capacity assessment by ergospirometry. At the end of the study, there was a significant improvement in quality of life and potential improvement in functional capacity assessed by peak VO_2 in the group that underwent training ($p < 0.05$). There were no statistically significant differences in left ventricular ejection fraction, symptom scores (MDASI-HF), or physical activity level. The sample size and the difficulty in randomization to a supervised program constituted important limitations of this study.[36]

In a retrospective study of 90 patients with cancer who had heart failure, 12 weeks of aerobic training did not result in an improvement in peak VO_2 or quality of life compared to the control group; however, the etiology of heart failure was categorized as ischemic or non-ischemic, and data such as type of cancer, disease stage, or antineoplastic therapy used were not collected.[37]

Future perspectives

Cardiotoxicity is one of the adverse effects of treatment that most compromises functional capacity and quality of life, with an impact on mortality, regardless of oncological prognosis.[38] However, there is a shortage of studies involving this patient population in the setting of cardiac rehabilitation.

Cardiac rehabilitation consists of a multidisciplinary program, based on physical exercise, with nutritional and psychological counseling.[39] It is highly recommended in patients with coronary artery disease and heart failure[40] owing to its numerous benefits, not only in improving physical capacity and quality of life, but also in reducing all-cause mortality and hospitalizations.[41] Based on this knowledge, the development of a more comprehensive model has been proposed to involve patients with cancer and high risk for developing cardiovascular diseases, in addition to patients with cardiotoxicity related to cancer therapies, using a multimodal approach, in a model known as Cardio-Oncology Rehabilitation (CORE).[42]

The incorporation of this rehabilitation model into traditional programs, however, requires knowledge of the specificities of each type of cancer. Exercise programs must also respect the individual characteristics of patients, such as functionality, disease stages, the presence of metastases, or contraindications.

Some cardiac rehabilitation centers have adapted to receive patients in the context of cardio-oncological rehabilitation,

including other professionals in their multidisciplinary teams and offering support in different phases of treatment.

One aspect that must be considered is that the few available cardiac rehabilitation services are still underused. It is estimated that only 20% to 30% of patients with an indication for cardiac rehabilitation are referred to a rehabilitation center.[43] Low adherence to supervised programs is another evident problem, associated with limited access due to distance from rehabilitation centers, costs, difficulty reconciling working hours, socioeconomic level, and frequent limitations due to the presence of other cancer-related symptoms. This is reflected in the difficulty in conducting studies and their results.

Conclusion

Undoubtedly, as with cardiovascular disease, physical exercise brings many benefits to patients with cancer at different disease stages or treatment phases. However, there is still a shortage of studies evaluating the therapeutic use of physical exercise in patients who develop heart failure as a consequence of treatment.

The use of structured physical exercise as an adjuvant therapy for manifest cardiotoxicity, nonetheless, appears to be indicatable and potentially beneficial.

Incorporating new models of cardiac rehabilitation into traditional programs, including patients at high risk for development or patients who already have manifest cardiotoxicity, and conducting more studies involving these patients are fundamental strategies for producing more robust evidence.

Author Contributions

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Ventricular Dysfunction and Heart Failure in Patients Undergoing Hematopoietic Stem Cell Transplant

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It has been known for a long time that Cyclophosphamide (Cy) for conditioning regimens in hematopoietic stem cell transplant (HSCT) can induce cardiotoxicity.[1] We have been learning in cardio-oncology that the best practice is to identify the risks of cardiotoxicity and, when possible, minimize them before the exposure. Several factors contribute to define cardiovascular toxicity risks including the type of transplant, age at transplant, hypertension, diabetes mellitus, dyslipidemia, and current smoking. Multiple uncontrolled preexisting cardiovascular conditions such as atrial fibrillation or atrial flutter, node sinus disease, ventricular arrhythmias, coronary artery disease, valve diseases and heart failure with reduced ejection fraction may also contribute to cardiotoxicity. So, it is important to know about the disease severity at the time of transplantation and probability of relapse, which may be correlated with increased exposure to other cardiotoxic chemotherapy drugs and radiotherapy before HSCT.

There are mainly two types of HSCT: (1) autologous transplantation, in which the patient receives his/her own progenitor cells, and the cardiotoxicity is mainly attributed to the direct toxic effects of the conditioning regimen; and (2) allogeneic transplantation in which the patient receives cells from another individual who may be fully or partially compatible. The allogeneic transplantation is known to have a higher risk of cardiotoxicity because in addition to the conditioning toxic effects, there are indirect effects of cytokines released in graft-versus-host disease and a possible direct cardiotoxicity through donor T-cell infiltration into the myocardium with subsequent inflammation leading to cardiac dysfunction.[2] The HSCT has six stages as presented in Figure 1: pre-transplant, conditioning phase (when the patient receives chemotherapy and often radiotherapy to eliminate the recipient's bone marrow, infusion, aplasia, recovery and post-transplant stage. In pre-transplant, the cardio-oncologist must perform a comprehensive assessment of the risk factors for cardiotoxicity. Clinical history and physical examination, electrocardiogram, laboratory tests including T troponin and brain natriuretic peptide (BNP) (or N-terminal-proBNP NTproBNP), X-ray or, preferably, chest computed tomography, strain echocardiogram and spirometry test are essentials for a good evaluation.[3] Rhythm and hemodynamic changes are described in the infusion stage, usually quick and benign as sinus tachycardia or bradycardia, hypotension or hypertension, but also serious ones as a total AV block. These changes seem to be caused by dimethyl sulfoxide, a cryoprotectant, but there is still not enough data to support this hypothesis.[4] Many infectious complications may occur in the aplasia phase, such as myocarditis due to viral reactivation and sepsis-induced cardiomyopathy. The differential diagnosis between these conditions and cardiotoxicity can be challenging.

Cardiovascular risk factors, exposure to cardiotoxic agents, high cumulative dose (anthracyclines ≥250mg/m^2) chemotherapy administered during conditioning (which is rare), with or without radiation, contribute synergistically to cardiovascular morbidity and mortality. Oxidative stress, cycling by iron complexes and genetic variants have been suggested as mechanisms. Women are twice as likely as men to develop heart failure. Cardiac adverse events have been attributed to different components of HSCT itself such as total body ablative radiation therapy combined with a multi-drug conditioning regimen.[5]

Congestive heart failure is generally considered a long-term complication of HSCT, but a new onset left ventricular dysfunction can also occur in the short term. Early-onset heart failure occurs in approximately 0.4% to 2.2% of patients, occurring within 100 days after allogeneic HSCT and as early as four days after Cy infusion.[2,6] It was defined as a decrease in left ventricular function a reduction ≥10% from baseline left ventricular function and of ≤53% after HSCT, irrespective of baseline left ventricular function, which was assessed before the first chemotherapy session.

The five-year incidence of congestive heart failure was reported to be 4.8%, rising to 9.1% at 15 years. The transplant is usually contraindicated in patients with a pre-transplant left ventricular ejection fraction less than 35%, especially because of the association between pre-transplant ejection fraction and short-term outcomes.[7] Cardiovascular disease, unless very severe, should not be a specific barrier to indicate HSCT and can often be managed by a multidisciplinary team before the procedure. Periodic monitoring of cardiac function using global longitudinal strain or left ventricular ejection fraction in echocardiography and serum biomarkers is recommended to detect early changes in cardiac status before irreversible cardiac complications develop.[8]

Keywords

Insuficiência Cardíaca; Cardiotoxicidade; Transplante; Medula Óssea

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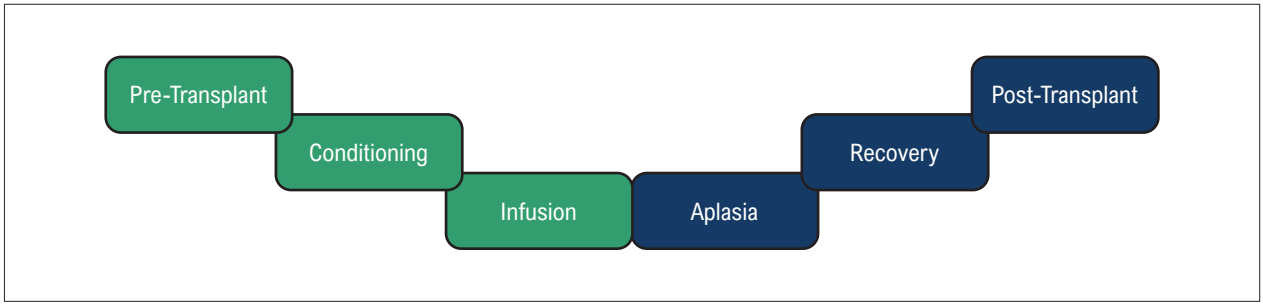

Figure 1 – *Stages of hematopoietic stem cell transplantation.*

Clinical benefits with prophylactic usage of beta-blockers or angiotensin-converting enzyme inhibitors have not been fully established in preventing cardiotoxicity in HSCT.

In summary, patients who are candidates for HSCT must be evaluated in advance by a cardio-oncologist or an expert cardiologist, have their cardiovascular and metabolic status optimized and followed up during the various stages of the transplant, and during a mid- and long-term follow-up plan.

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Hypertension in Patients with Cancer as a Predictor of Ventricular Dysfunction

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Hypertension is the most prevalent comorbidity (38%) in patients with cancer and is considered an important modifiable risk factor for the development of cardiovascular events, including heart failure (HF). Importantly, hypertension may worsen the prognosis of patients with cancer and the severity of some types of cancer.[1,2] In addition, cancer treatments may aggravate pre-existing or even cause new hypertension,[1,2] making the role of this risk factor even more complex and multifaceted.

It is important to note that the use of cardiotoxic drugs in association with an important and prevalent cardiovascular risk factor such as hypertension makes HF a common final pathway of damage to the heart. The association between hypertension, especially if poorly controlled, and increased risk of chemotherapy-induced cardiomyopathy and HF[1,3] has been demonstrated since studies with doxorubicin in the 1970s. In a retrospective study involving patients with lymphoma undergoing doxorubicin chemotherapy, the drug was an independent predictor of HF development, even after adjusting for risk factors. In addition, among patients undergoing treatment, hypertension was strongly associated with the development of HF.[4] Thus, managing this complex interaction should be a priority for patients with cancer.

Cancer and hypertension are intertwined from shared pathophysiological mechanisms, such as inflammation and oxidative stress, to common risk factors including smoking, diabetes, and obesity.[1] Some anticancer therapies (ACT), adjuvant therapies, anxiety, and pain may directly contribute to the increase in hypertension incidence or indirectly mediate its development through adverse effects such as nephrotoxicity. Furthermore, different factors related to cancer treatment can act as confounders for the measurement of blood pressure (BP). Conversely, hypertension may be associated with increased incidence or worsening of some types of cancer, such as renal cell cancer. In a prospective cohort of 577,800 adults followed for 12 years, hypertension was associated with higher cancer incidence in men and higher cancer mortality in men and women.[1]

Several classes of oncologic drugs have been associated with the development or exacerbation of hypertension, which is the most common serious adverse event in patients with cancer undergoing chemotherapy.[5] The increase in BP may occur in the first weeks of treatment and can be considered a predictor of therapeutic efficacy. Retrospective data suggest that at least one-third of patients develop hypertension during follow-up,[6] with renal, gastric, and ovarian cancer being more associated with moderate and severe hypertension. Considering that treatment is time-sensitive, ACT should be maintained and the use of antihypertensives should be optimized. BP normalization typically occurs after discontinuation of treatment, allowing de-escalation or even discontinuation of anti-hypertensive drugs.

Among drugs that can potentially contribute to the onset or worsening of hypertension are vascular endothelial growth factor (VEGF) inhibitors, some tyrosine kinase inhibitors (TKI), abiraterone, enzalutamide, etc. This association has been best described for VEGF inhibitors and TKI. In VEGF inhibitors, hypertension (which is observed in almost 50% of patients) results from a reduction in nitric oxide production and angiogenesis, leading to increased vascular resistance as well as fluid retention due to impaired natriuresis and endothelin-1–mediated vasoconstriction.[7] As for TKI, a meta-analysis showed a 3.8-fold greater risk of hypertension, in addition to a 1.7-fold greater risk of cardiac ischemia and a 2.5-fold greater risk of left ventricular dysfunction.[3,7] Adjuvant therapies, such as corticosteroids, erythropoietin, nonsteroidal anti-inflammatory drugs, and radiotherapy, may also contribute to hypertension development through different mechanisms. Therefore, careful monitoring is required when these therapies are part of the cancer treatment regimen.

Besides the rapid development of hypertension during the treatment, several ACT are associated with late hypertension, with a higher prevalence among survivors (which may exceed 70% at age 50,[8] with adjusted rates 2.6 times higher than expected). In addition, survivors are 1.6 times more likely to be prescribed antihypertensive drugs than siblings without a history of cancer.[9] In this complex scenario, out-of-office BP monitoring in patients with cancer diagnosed with hypertension is advised at the beginning of cancer and hypertension treatments, as well as after intensification of treatment. Factors such as pain, fear, and anxiety can interfere with the assessment, which is also influenced by clinical, oncological, and pharmacological variables.

Keywords

Hypertension; Cancer; Heart Failure; Anticancer therapy; Anti- Antihypertensives; Prognostic Assessment

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The number of robust studies prospectively testing the influence of chemotherapy drugs on the efficacy of different classes of antihypertensive drugs is limited. In general, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and dihydropyridine calcium channel blockers are considered first-line drugs, as in hypertension in general. Adding a second agent is preferable to increasing the dose, reducing the incidence of adverse effects. In this case, diuretics and second-generation beta-blockers are good options.[2,3] Attention should be paid to avoid specific drug interactions, such as: a) prescription of nondihydropyridine calcium channel blockers during chemotherapy with VEGF inhibitors, due to inhibition of cytochrome P450 3A4;[10] b) possible bradycardia with the use of beta-blockers or nondihydropyridine calcium channel blockers together with TKI; c) increase in the concentration of P-glycoprotein inhibitor chemotherapy drugs by beta-blockers; d) increase in the concentration of angiotensin receptor blockers and calcium channel blockers by chemotherapy drugs that inhibit CYP2C9 and CYP3A4, among others.[10,11]

Due to the lack of clinical and laboratory evidence on optimal BP control in patients with hypertension and cancer, recommendations are divergent. The criteria used by oncologists for dose management or discontinuation of therapies are from the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0,[10] a descriptive terminology for gradually reporting adverse events.[1,5] However, we understand that, when treating hypertension, each case should be considered individually, taking into the account the oncological context and the prognosis to guide the therapeutical approach. Given that patients with cancer require multidisciplinary care, the multidisciplinary team should work together to find the best strategy.

For better management of hypertension in patients with cancer, we suggest that cardiovascular risk stratification and optimization of treatment of underlying comorbidities be conducted from the first assessment. For the treatment of cancer-associated hypertension, nonpharmacological therapies should be initially considered, including low-sodium diet, regular physical activity, smoking cessation, weight control, and other changes in health determinants.[3] The pharmacological approach should follow recommendations described in international guidelines but should also be individualized according to the specificities of each patient (Figure 1). For example, in patients on VEGF inhibitors or with proteinuria, drugs that act on the renin-angiotensin system should be prioritized as first choice; in patients susceptible to diarrhea, diuretics should be avoided due to loss of electrolytes and the risk of dehydration.[3]

Personal aspects should always be considered, such as in patients on VEGF inhibitors, in whom systolic and diastolic BP may increase in the first weeks of treatment which is, in fact, more common in the first cycles. Therefore, daily home BP monitoring is recommended in the first cycle, after each increase of ACT dose, and then every 2-3 weeks.[2,3] BP increase in response to chemotherapy is an independent predictor of better treatment outcomes. Therefore, chemotherapy should not be interrupted, and hypertension should be treated aiming at ideal BP targets. Thus, individualized decision-making should consider pharmacological aspects such as those previously described, as well as specific aspects of the disease, previous treatments, clinical conditions, and pre-existing risk factors.

In the setting of cancer treatment, the interaction between hypertension, whether pre-existing or related to chemotherapy, and the development of HF is equally complex. In nonhypertensive patients with a history of colorectal, stomach, or breast cancer, BP measurement during treatment was associated with HF incidence, with an almost 2-fold increased risk in patients with stage 2 cancer.[12] Prospective data demonstrated that the presence of hypertension in cancer survivors increases the relative risk of cardiac events, including HF (relative risk = 19.4), irrespective of the risk associated with ATC.[12] Despite the need for further studies for better management, baseline cardiovascular assessment and multidisciplinary teamwork are essential for prevention and treatment guided by HF guidelines.

In conclusion, patients with cancer require careful BP monitoring by health professionals throughout their treatment and after its completion, in addition to a more careful multidisciplinary follow-up from a cardiovascular perspective, with defined quality parameters and in accordance with guideline recommendations. Such strategies aim to reduce the risk of end-organ damage, with an impact on morbidity and mortality, especially HF.

Author Contributions

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Ethics approval and consent to participate

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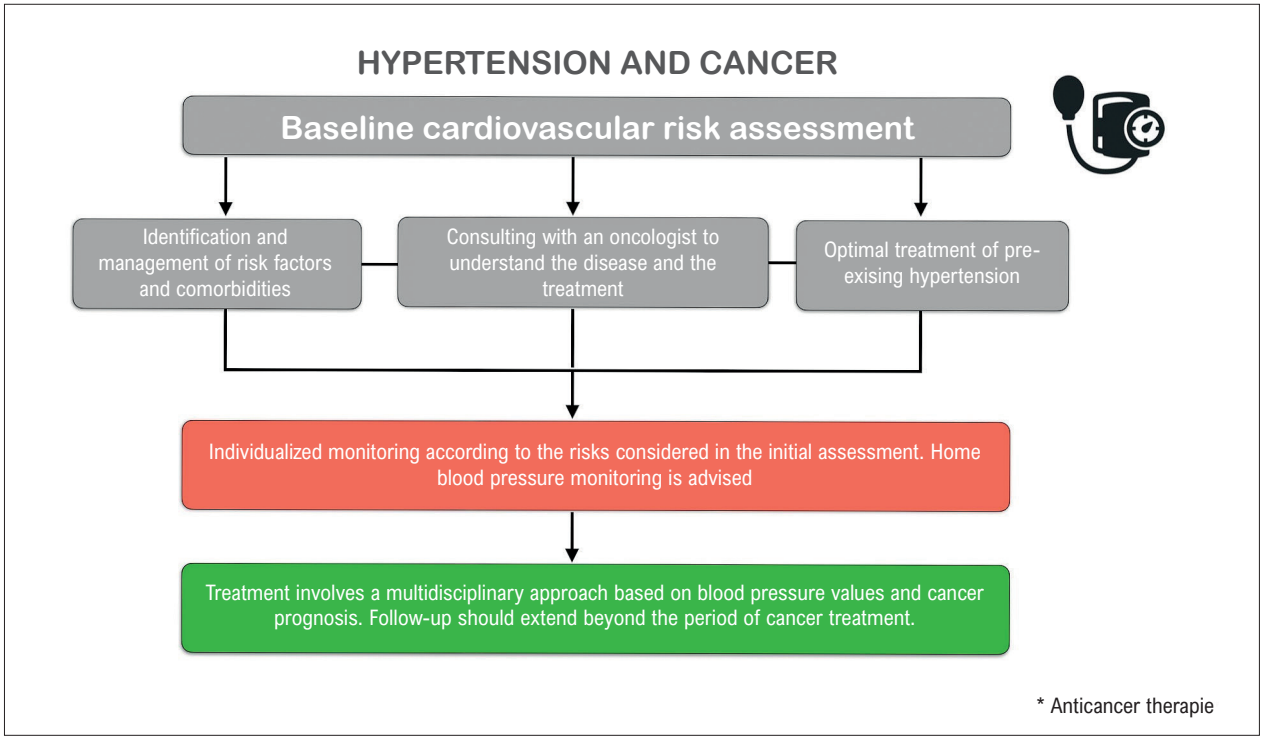

Figure 1 – *Flow diagram of recommendations for hypertension management in patients with cancer.*

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How to Anticoagulate Patients with Heart Failure and Cancer?

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Patients with cancer have a high risk of deep vein thrombosis and pulmonary embolism, as well as a risk of developing atrial fibrillation (AF) secondary to antineoplastic treatment. These events have a poor prognosis and depend on factors related to the tumor and the ongoing therapy. They are usually elevated during the first 6 months of treatment.[1]

Many neoplasms may be associated with paroxysmal, persistent, or permanent AF in patients with cancer, and AF may arise as a direct effect of the cancer (extracardiac or intracardiac compression) or more frequently after surgery, as a complication of thoracic (postoperative thoracic or esophageal surgery) or abdominal (colon surgery) surgery. AF can also arise during or after chemotherapy or radiation therapy. This latter condition is underestimated, since information on drug-related AF is derived from case reports.[2]

Antineoplastic drugs can produce non-valvular AF by several mechanisms, and the most common are the release of pro-inflammatory proteins (cytokines), calcium homeostasis changes, and direct damage to the myocardium. Anthracyclines, for example, reduce the antioxidant effect of cardiomyocytes, and they increase vagal and adrenergic tonus, due to hypotension, myocardial ischemia, and hydroelectrolytic disturbances. These mechanisms are also induced by alkylating agents, gencitabine, fluorouracil, antimetabolic agents, docetaxel, rituximab, paclitaxel, and alemtuzumab.[3]

AF poses a challenge to managing antineoplastic therapy and predicting prognosis of cancer patients.[4] Anticoagulation in patients with AF becomes a major problem due to imbalance between the thromboembolic and bleeding risks that are high, due to both the cancer itself and the adverse effects of its treatment.[2]

New anticoagulant drugs have emerged. In 2009, dabigatran was the first direct oral anticoagulant (DOAC), a direct thrombin inhibitor as an anticoagulant alternative. Later came the factor Xa inhibitors, rivaroxaban, edoxaban, and apixaban that brought clinical studies of efficacy and safety, with the benefits that they do not need monitoring, and they have fewer drug interactions and better safety profile. Anti-Xa DOACs have presented studies in the oncology patient population (SELECT-D, Hokusai Cancer, and Caravaggio), which have made their use in anticoagulation therapy in cancer patients feasible and safe.[5-7]

Apixaban has a dosage of 2 daily doses, a half-life of 12 hours, a maximum plasma concentration of 4 hours, and a renal clearance of 27%. It is mainly metabolized by CYP3A4.[5] Edoxaban has a dosage of 1 dose per day; its absorption and clearance depend on P-gp, and in cases of possible interactions, a 50% dose reduction is advocated. It is eliminated mainly by the kidneys (50%).[6] Rivaroxaban is the DOAC with the highest oral bioavailability (≥ 80%). Unlike other DOACs, its absorption requires food intake. Like apixaban, it is also metabolized mainly by CYP3A4/5 (~ 18%). Its renal excretion is about 36%.[7] Knowing the metabolization of DOACs is important, because most antineoplastic drugs are metabolized by CYP, and their interaction can lead to a higher hemorrhagic or thrombotic risk depending on whether these drugs act as inducers (increase the risk of recurrence) or inhibitors (bleeders). Similar effects occur with P-gp inhibitor drugs.[8]

Heart failure and AF are closely related. These patients have even worse symptoms and poorer prognosis. When considering the cardiotoxic effects of antineoplastic therapies, this association in cancer patients adds an additional risk and a challenge to anticoagulant therapy.[9] We must evaluate not only the antineoplastic therapies, but also those that are used for heart failure. For example, amiodarone increases bleeding risk due to changes in plasma concentrations in concomitant use with apixaban and edoxaban; antiplatelet aggregating drugs increase bleeding risk.[8,10,11]

There is still discussion regarding prospects of widespread use among patients with AF or venous thromboembolism and cancer in addition to chronic kidney disease with creatinine clearance below 15 mL/min and/or undergoing hemodialysis. Apixaban, edoxaban, and rivaroxaban, through small clinical and pharmacokinetic studies, are the oral anticoagulants that have already been approved by the United States Food and Drug Administration for use in this patient profile.[12]

When establishing an anticoagulant therapy for these patients, we should consider their primary neoplasm, cardiovascular risks, the therapies that are being administered, the moment in their oncologic therapy, surgeries, chemotherapies, hemorrhagic and thromboembolic risk, and especially the drugs that are involved. Only after studying those coefficients, we propose an anticoagulant therapy that is more effective, safer, and individualized.

Unfortunately, we still do not have a specific risk score for cardioembolic events in patients with cancer and AF who require anticoagulation, such as the one used in the general population, CHADSVASC. Some small studies reinforce, however, that even patients with a CHADSVASC of 1 may

Keywords

Anticoagulation; Cancer; Heart Failure

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be at increased risk of these phenomena, underscoring the importance of not failing anticoagulation for this cancer population.[13]

Considering the pharmacological characteristics of anti-Xa drugs, we observed that edoxaban has a safer profile during antineoplastic therapy due to the lower risk of bleeding and great applicability in the elderly. Apixaban is safer, with respect to bleeding risk, and rivaroxaban has more studies regarding extended anticoagulation therapies. However, the professional's experience in handling anticoagulant drugs is extremely important when prescribing them.

Conclusion

Anticoagulation in oncologic patients is a huge challenge, and we must always consider the risks and benefits of this management. However, with the prescription of DOACs, it becomes easier, safer, and more effective. When we individualize a patient's therapy, according to the oncologic treatment, we can purpose the most appropriated strategy. We reinforce that, because of a high complex profile with several treatments, patients must be reevaluated periodically. In this way, we will further good medical practice.

Author Contributions

Conception and design of the research: Renni MJP; Acquisition of data; Analysis and interpretation of the data; Writing of the manuscript; Critical revision of the manuscript for important intellectual content: Renni MJP, Marinho TAS.

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Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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Preoperative Evaluation and Perioperative Complications in Patients with Cancer and Ventricular Dysfunction

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During cancer treatment, surgery may be indicated for patients with diverse purposes, such as diagnosis, staging, oncologic cure, palliative treatment, support, or restorative treatment. Oncologic surgery may be conducted as an initial cancer treatment or after conducting treatments such as chemotherapy or radiotherapy, thus underscoring the cardiotoxic potential of different cancer therapies.[1]

In patients undergoing non-cardiac surgeries, the prevalence of comorbidities, the clinical condition before surgery, and factors inherent to the surgical procedure, such as urgency, magnitude, type, and duration, in addition to local experience, infrastructure, and the surgical team contribute to the risk of perioperative complications.[2] In oncologic surgery, risk factors include the type and stage of the tumor and concomitant cancer therapies.

It is worth emphasizing that there is a shortage of robust evidence, such as randomized clinical trials, to validate the indications of the main guidelines for evaluation and perioperative management of non-cardiac surgeries, and this scenario is more evident when dealing with oncologic surgeries.[2,3]

Preoperative clinical evaluation before oncologic surgery is important; however, it should not delay the surgical procedure. In this context, cardio-oncology plays a role in minimizing risks, but it avoids depriving patients of the indicated cancer treatment, in this case surgery. In rare situations, when facing a high surgical risk, it is possible to discuss with the oncologist whether a non-surgical treatment option that also offers improved prognosis is available.

In recent decades, several preoperative risk scores have been developed, and they have been used in the preoperative assessment of patients undergoing non-cardiac surgery.[4-6] However, it is evident that there is a low representation of patients with cancer in the studies that validated these clinical scores, in addition to a small number of studies that have evaluated surgeries for specific tumors. Recently, the Heart Failure Association and the International Cardio-Oncology Society proposed an instrument for assessing cardiac risk in cancer treatment based on clinical and laboratory factors, in addition to previous cardiotoxic treatments performed.[7]

In patients with cancer, aspects such as frailty and performance status may represent relevant aspects in the preoperative assessment of patients, and scores that specifically assess them may be useful.[3,8,9]

Ventricular dysfunction is a risk factor for the occurrence of peri- and postoperative complications, and it can occur due to different causes at all ages. This condition increases the morbidity and mortality associated with the surgical procedure.[10] Surgical procedures have the potential to aggravate this underlying condition. This can be avoided by implementing appropriate risk stratification before surgery and optimizing perioperative therapy with the adoption of measures recommended in heart failure guidelines.[11]

Tests such as electrocardiogram, echocardiogram, and biomarkers assist in the preoperative evaluation and postoperative management of patients with ventricular dysfunction.[12] Other tests, such as those associated with stress, magnetic resonance imaging, tomography, or even coronary angiography, should only be performed in an exceptional, individualized manner and in contexts where they can potentially modify the cardiological or oncological practice, thus avoiding delays in surgery or unnecessary emotional stress for patients.

It is recommended to control risk and lifestyle factors, such as smoking, obesity, blood pressure management, diabetes, and dyslipidemia, for all patients with the aim of reducing peri- and postoperative complications.[7]

The type of anesthesia and the drugs used during anesthesia warrant attention in patients with ventricular dysfunction. Volume and perfusion status should be assessed regularly. A multidisciplinary team with specialists in ventricular assist devices must necessarily be involved in the perioperative management of patients who require mechanical circulatory support.

Rhythm and conduction disorders may be present in patients with ventricular dysfunction who are undergoing surgery. During preoperative evaluation, it is necessary to consider the risk of symptomatic bradyarrhythmias and the need for artificial cardiac stimulation (transvenous and/or transcutaneous pacemaker). Patients with cancer are also

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Neoplasms; Preoperative Period; Ventricular Dysfunction

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susceptible to tachyarrhythmias, especially supraventricular ones. Special mention should be made of cardiac arrhythmias during the postoperative period in these patients, especially atrial fibrillation and thromboembolic events. Specific aspects should be taken into account in the management of these complications, such as drug interactions and risk of bleeding, mainly related to the medications in use, tumor type and stage, and comorbidities.[13]

The surgical technique can influence patient outcomes; therefore, in patients with cancer and ventricular dysfunction, if possible, priority is given to using less invasive techniques and performing surgical procedures with a team and center experienced in oncologic surgery and high-risk patients. These measures aim to optimize the surgical result by reducing the chances of prolonging the surgical procedure or unnecessary additional procedures.

Patient participation in decision-making is recommended, but unfortunately studies have indicated a relatively high prevalence of limited level of schooling in patients with cardiovascular diseases, especially heart failure,[14] which is associated with worse outcomes.[15] It is, therefore, evident that specific actions are needed for these patients when undergoing oncologic surgery, so that they are aware of the risk-benefit ratio of the available therapeutic options.

The occurrence of various postoperative complications is increased both in patients with cancer and in patients with ventricular dysfunction. In the presence of heart failure, with or without symptoms, even minor postoperative complications may be poorly tolerated, reducing medium- and long-term survival.[16]

The organization of multidisciplinary cardio-oncology services makes possible the global and individualized assessment of patients with ventricular dysfunction who are candidates for oncologic surgery, and it optimizes pre-, peri- and postoperative management by implementing practices based on specific guidelines for this context.[17]

It is, therefore, worth emphasizing the need for further studies in patients with cancer and ventricular dysfunction in specific clinical scenarios related to tumor type and stage. Only in this way will it be possible to base clinical practice on more robust evidence than that which is currently available for the management of these patients.

Author Contributions

Conception and design of the research: Issa AC; Acquisition of data: Issa AC, Zagni G, Vidotti V; Analysis and interpretation of the data: Issa AC, Guimarães T; Writing of the manuscript: Issa AC, Vidotti V, Santos M; Critical revision of the manuscript for important intellectual content: Issa AC, Zagni G, Vidotti V, Guimarães T, Santos M, Silva CMPDC.

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Case Report

Heart Transplantation in Patients with Chemotherapy-Induced Cardiotoxicity

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Abstract

We report 3 cases of heart transplantation in adults due to chemotherapy-induced cardiotoxicity in a transplant center in Rio de Janeiro, Brazil. All patients received anthracyclines during cancer treatment. We reviewed and discussed the cases with data from the literature, addressing the importance of early diagnosis and treatment of heart failure in cancer survivors.

Introduction

The survival rates of adults and children with cancer have improved significantly due to advances in treatment and diagnosis. Therefore, many long-term survivors have been exposed to anticancer treatment (ACT). Certain chemotherapy drugs induce an increased risk of developing cardiovascular complications. Lesion incidence and severity depend on the chemotherapy drug, cumulative dose, presence of previous heart disease, comorbidities, and use of other ACTs.[1] In addition to secondary malignancies, childhood cancer survivors are more prone to cardiovascular death.[2]

Ventricular dysfunction is one of the most serious complications of cancer treatment, with high morbidity and mortality rates. Chronic cardiomyopathy leading to severe heart failure (HF) secondary to chemotherapy-induced cardiotoxicity is classically described. Heart transplantation (HT) remains the best treatment for refractory HF.[3]

The objective of this study was to report the experience of the first HT center in Rio de Janeiro, Brazil, with 3 cases of chemotherapy-induced cardiotoxicity progressing to advanced HF and requiring HT. The decision on whether to perform HT was made by the cardiology and oncology teams, in the absence of active malignancy and risk of recurrence.

Case 1

A White male patient was diagnosed with testicular cancer (surgically resected) and acute lymphoblastic leukemia at 9 months of age in April 1994. The patient was treated according to the St Jude R11 protocol with the following induction agents: daunorubicin, vincristine, cytarabine, prednisone, and methotrexate. Maintenance therapy included cyclophosphamide, vincristine, and methotrexate, among others. Treatment was intensified with vincristine and daunorubicin. Total dose of daunorubicin was 164 mg. Induction therapy was terminated in August 1994 and maintenance therapy in October 1996, with complete remission. At 15 years of age, in 2008, the patient suffered a cardioembolic ischemic stroke and was diagnosed with cardiomyopathy. The patient had hypothyroidism and was on levothyroxine. He presented at the National Cardiology Institute (Instituto Nacional de Cardiologia, INC) in Rio de Janeiro, Brazil, in February 2011 with complaints of tiredness and dyspnea on vigorous exertion for approximately 5 months. The patient remained in New York Heart Association (NYHA) functional class II until 2012 and underwent a HT at 21 years of age. Pre-transplant echocardiography showed Teicholz ejection fraction (EF) = 29%, end diastolic volume (EDV) = 166.6 mL, end systolic volume (ESV) = 118.2 mL, left ventricular (LV) systolic mass = 148.8 g, pulmonary artery systolic pressure (PASP) = 36 mmHg, enlargement of the four cardiac chambers, severe global LV systolic dysfunction with diffuse hypokinesia, severe right ventricular (RV) contractile dysfunction, moderate functional mitral insufficiency (MI), tricuspid insufficiency (TI), and moderate pericardial effusion. In the postoperative period, the patient had worsening of renal function and required hemodialysis, with subsequent recovery of renal function and hospital discharge 32 days after the HT. The echocardiogram showed Teicholz EF = 71.4%, PASP = 48 mmHg, mild biatrial and RV enlargement, RV systolic dysfunction, and mild MI and TI. He was readmitted for cytomegalovirus colitis and treated with ganciclovir. During readmission, he required pleural and pericardial drainage. The patient remains in outpatient treatment.

Case 2

A Black female patient was diagnosed with osteosarcoma at 14 years of age in 2012. The patient underwent surgical resection of the tumor and chemotherapy (cisplatin, doxorubicin, and methotrexate). In 2013, she was diagnosed with dilated cardiomyopathy and HF with reduced EF. She evolved to dialysis treatment due to chronic kidney disease due to treatment with multiple antimicrobial regimens for osteomyelitis as well as amputation of the left leg. An echocardiogram conducted in May 2019 showed EF = 30%, diffuse hypokinesia, thrombus in the inferoapical region of the LV, mild MI, and PASP = 23 mmHg. She remained in NYHA functional class I until 2018. The patient started

Keywords

Heart Transplantation; Cardiotoxicity; Heart Failure

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treatment at INC in June 2019 due to worsening of symptoms 3 months earlier, during pregnancy. At 23 years of age, after 2 months of hospitalization, in INTERMACS 3 and renal failure classified as stage 5 according to the Kidney Disease: Improving Global Outcomes, she underwent a combined heart and kidney transplant from a single donor. Orthotopic HT was initially performed, followed by heterotopic kidney transplantation. The patient was discharged from hospital 41 days after the transplant and remains in outpatient treatment.

Case 3

A Black female patient was diagnosed with osteosarcoma in the left femur in 2011 at 21 years of age. She underwent surgical resection of the tumor, knee prosthesis implantation, and 3 cycles of chemotherapy with neoadjuvant doxorubicin, with no metastasis. After surgery, the patient underwent 3 more cycles of chemotherapy. The treatment was terminated in 2012, when she was diagnosed with HF after complaining of intense tiredness. The patient attended follow-up visits close to home but had difficulty adhering to treatment due to the side effects of medications. She started treatment at INC in December 2018 in NYHA functional class II. She was hospitalized for community-acquired pneumonia and decompensated HF and progressed with refractory cardiogenic shock, requiring intra-aortic balloon pump therapy and biventricular circulatory support. She also required massive blood transfusion and hemodialysis due to acute renal failure and underwent a simultaneous heart and kidney transplant in May 2009. Pre-transplant echocardiography revealed enlargement of right cavities and severe biventricular systolic dysfunction with diffuse hypokinesia. During surgery, after donor heart implantation, there was difficult-to-control bleeding in the aortic arch, progressive deterioration of RV function, and death.

Discussion

As ACTs continue to evolve, the number of cancer survivors increases, and 1% to 5% of them develop chemotherapy-induced cardiomyopathy (CCM).

We described 3 cases of CCM from the series of 135 HTs performed from 2007 to 2022 at the first HT center in Rio de Janeiro, Brazil. In a series of HTs between 1987 and 2011, 453 were due to CCM and 51,312 due to other causes.[4] Patients with CCM had improved survival without greater risk of death due to the malignancy. In another study conducted between 2000 and 2008, 232 HTs were conducted due to CCM and 8,890 due to other causes.[5]

The 3 patients included in this case report were in the third decade of life at the time of transplantation and received anthracyclines during cancer treatment. Although well-established chemotherapeutic drugs, anthracyclines are associated with cardiac dysfunction, cardiomyopathy, and HF. Anthracycline cardiotoxicity is considered an ongoing phenomenon that starts at the time of exposure to ACT and persists for months or years.

In the initial evaluation of patients receiving ACT, a thorough clinical history is imperative to define the follow-up strategy. Childhood cancer survivors are especially vulnerable to having limited information about their cancer and treatment because of their early age at diagnosis. Two of the 3 reported cases involved patients diagnosed with cancer in childhood. The importance of communication between the oncologist and cardiologist in patient follow-up is demonstrated.

Cardiac dysfunction related to ACT is a serious adverse event that may lead to severe HF and death. Early identification is essential, allowing implementation of appropriate treatment. Regular cardiac surveillance using cardiac biomarkers and/or cardiac imaging is recommended during and after treatment with anthracyclines; regularity depends on the initial assessment of cardiovascular risk. Symptoms of HF should be evaluated during clinical visits and, if necessary, the patient should be referred to the cardio-oncology department and/or to a specialist in HF and HT.[6]

Patients with advanced HF and a history of cancer who are considered free of disease may be candidates for mechanical circulatory support as bridge to transplantation, with the involvement of an oncologist.[7] Of the 3 reported cases, 2 required circulatory support. The waiting period after cancer remission for HT candidacy is based on patient-specific factors and tumor type.[8]

Severe CCM, when refractory to drug therapy, may require therapies destined for advanced HF, such as mechanical circulatory support and HT. The cardiologist and oncologist should work together to make a decision. Early diagnosis and referral of patients with advanced HF to specialized centers is essential.

Author Contributions

Conception and design of the research: Issa AFC, Guimarães TCF; Acquisition of data: Issa AFC, Vidotti V, Zagni G, Miranda J; Analysis and interpretation of the data: Issa AFC, Guimarães TCF, Vidotti V, Zagni G; Writing of the manuscript: Issa AFC, Guimarães TCF, Vidotti V, Santos M; Critical revision of the manuscript for important intellectual content: Issa AFC, Guimarães TCF, Vidotti V, Zagni G, Santos M, Miranda J.

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