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.

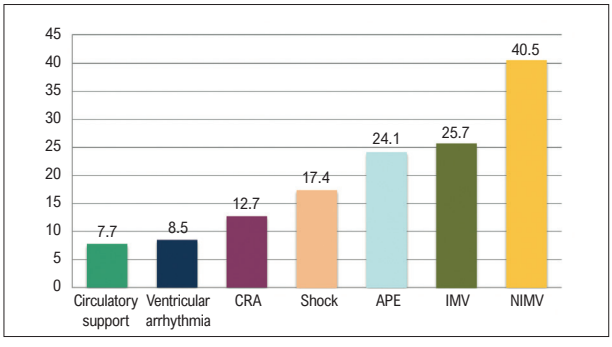

Figure 1 – *In-hospital complications in Takotsubo cardiomyopathy in the REMUTA registry. CRA: cardiorespiratory arrest; APE: acute pulmonary edema; IMV: invasive mechanical ventilation; NIMV: non-invasive mechanical ventilation.*[15]

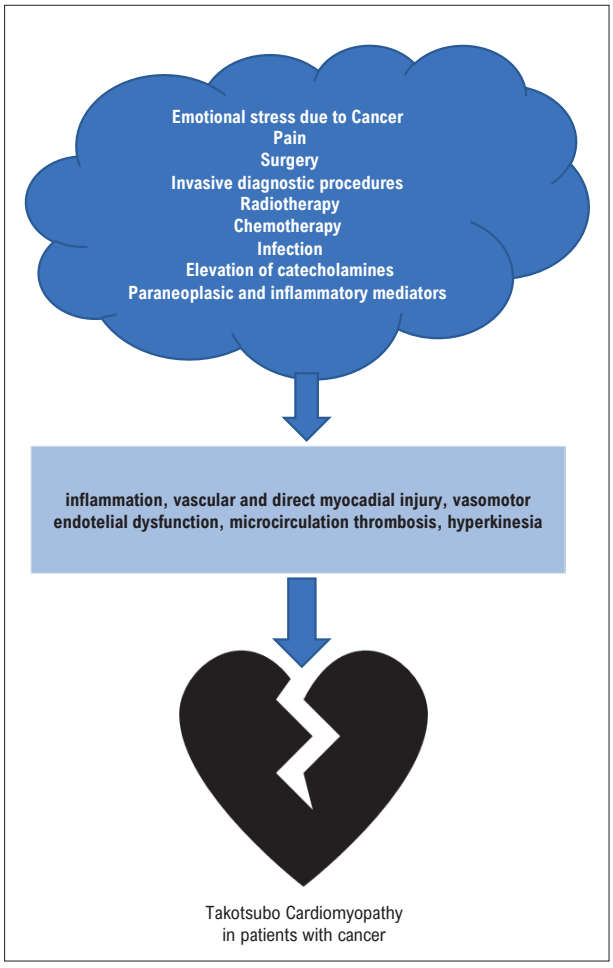

Figure 2 – *Potential triggers and proposed pathophysiological mechanisms involved in takotsubo cardiomyopathy in cancer patients*

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

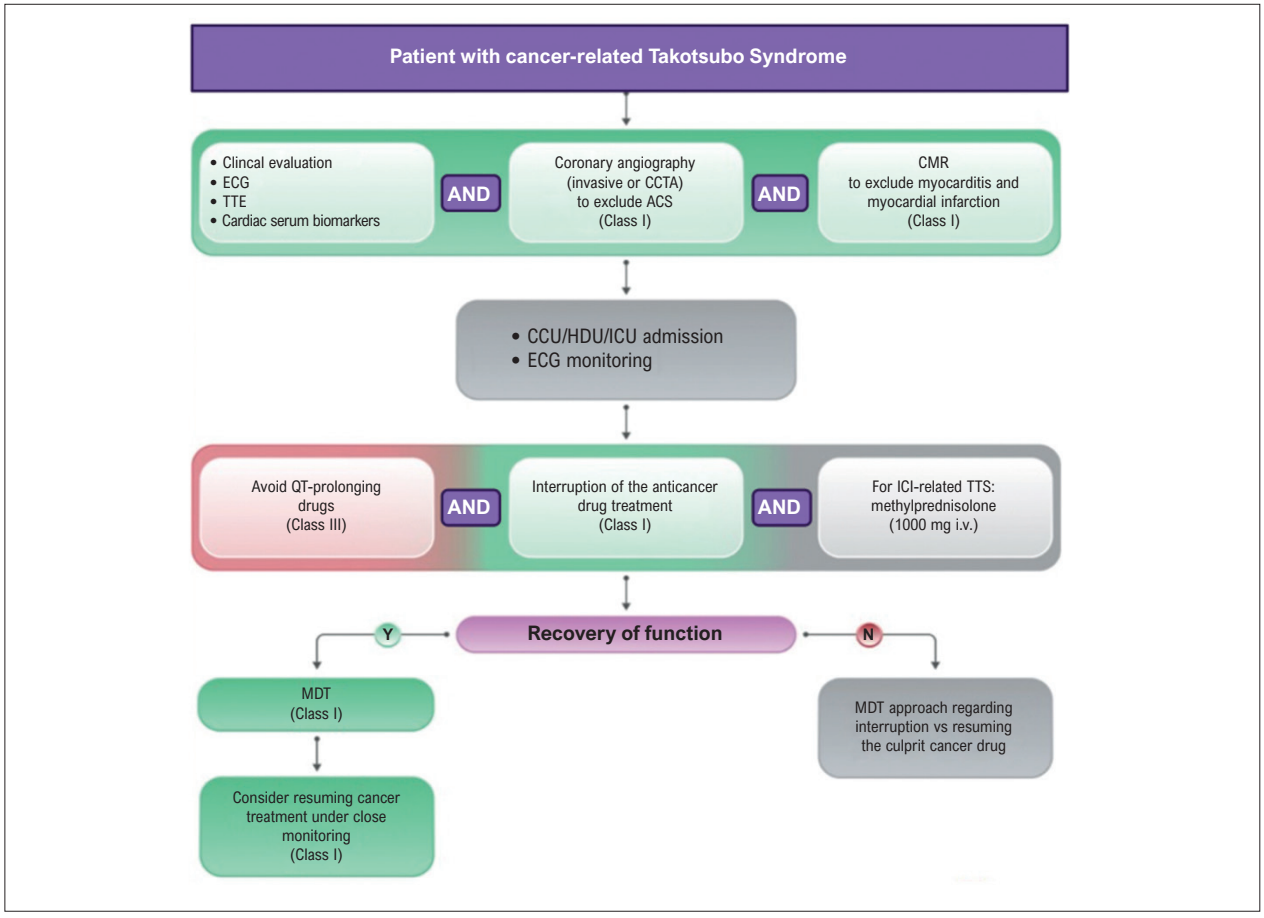

Figure 3 – *Diagnosis and management of cancer-related Takotsubo syndrome. ACS: acute coronary syndromes; CCTA: coronary computed tomography angiography; CCU: coronary care unit; CMR: cardiac magnetic resonance; ECG: electrocardiogram; HDU: high-dependency unit; ICI: immune checkpoint inhibitor; ICU: 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.

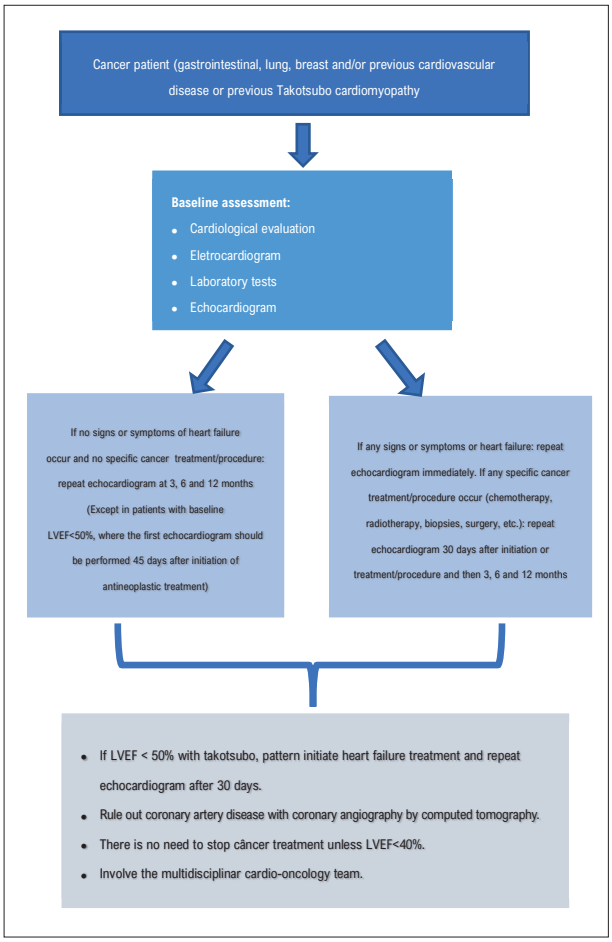

Figure 4 – *Clinical follow-up for cancer patients at higher risk of takotsubo cardiomyopathy. LVEF: left ventricular ejection fraction (original figure from the authors).*

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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