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

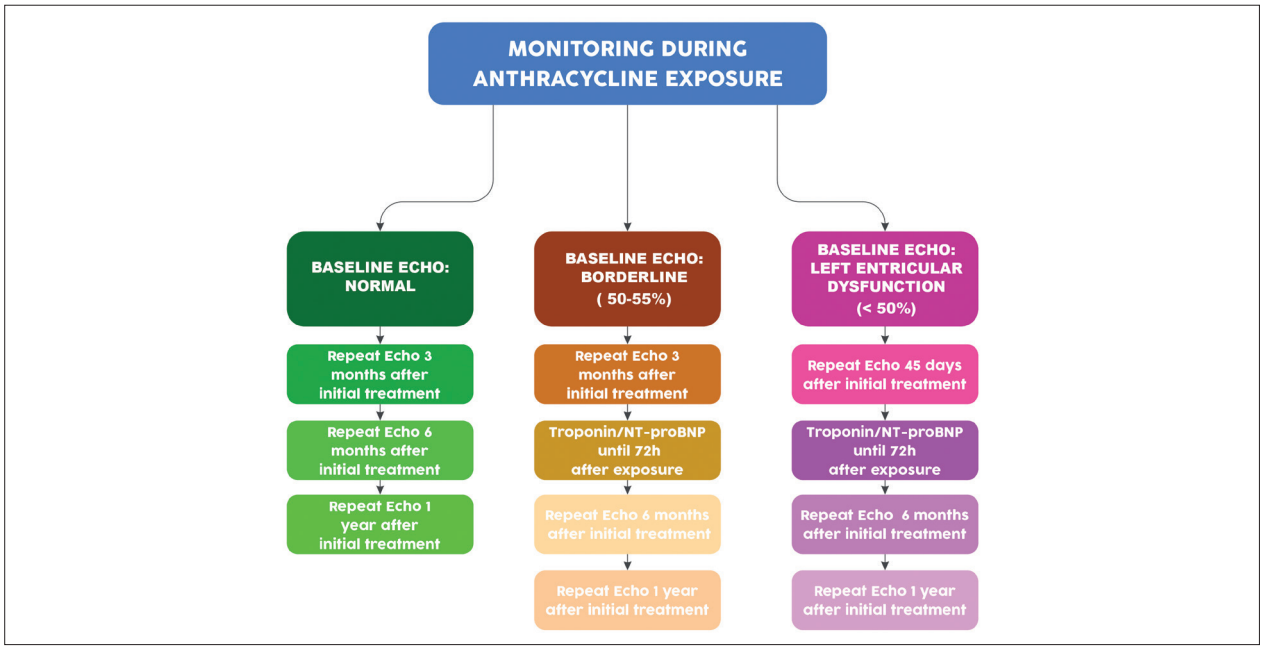

Figure 1 – *Echocardiographic monitoring and analysis of biomarkers in patients using anthracyclines suggested by the Brazilian Society of Cardiology. Echo: echocardiogram; NT-proBNP: N-terminal pro-B-type natriuretic peptide; QT: chemotherapy.*

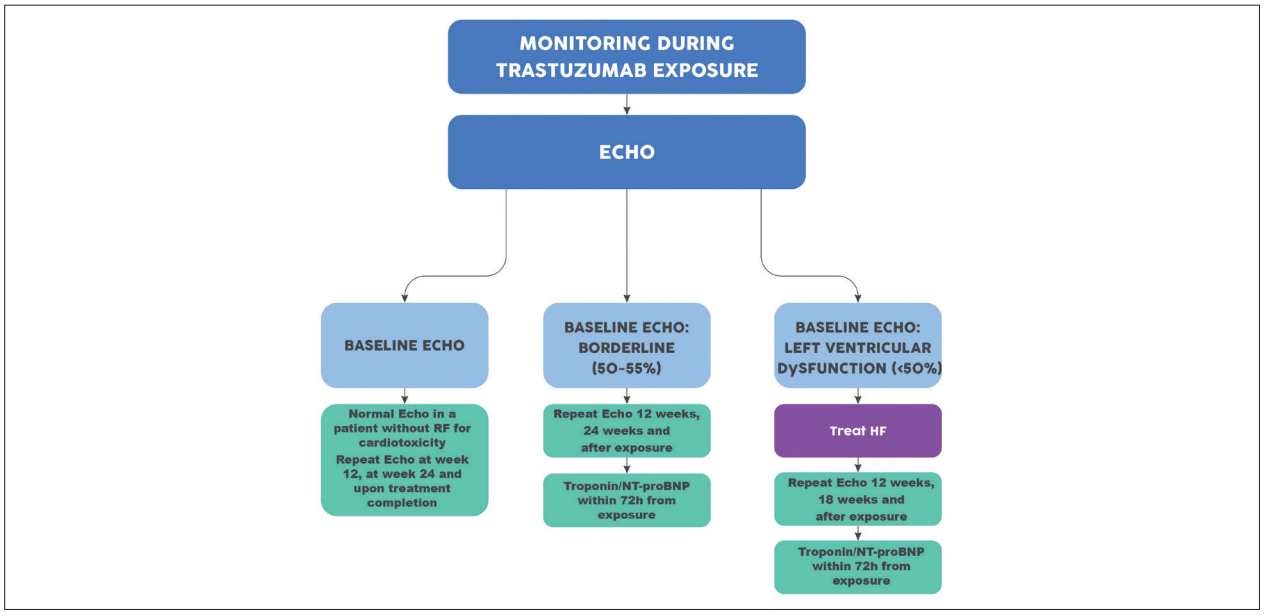

Figure 2 – *Echocardiographic monitoring and analysis of biomarkers in patients using anti-HER2 drugs suggested by the Brazilian Society of Cardiology. Echo: echocardiogram; HF: heart failure; NT-proBNP: N-terminal pro-B-type natriuretic peptide; RF: risk factors.*

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.

Potential conflict of interest

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This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

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

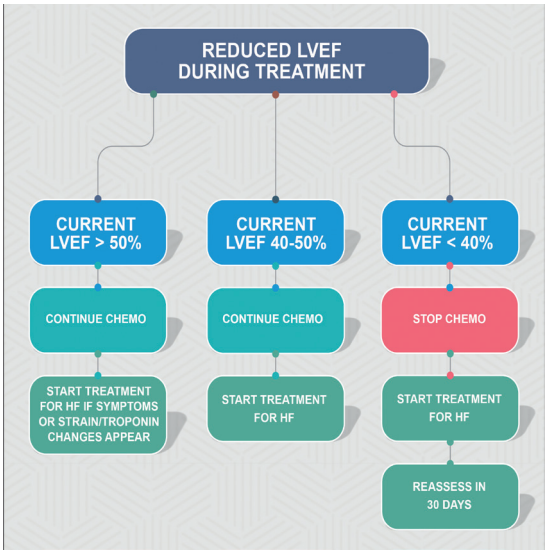

Figure 3 – *Algorithm of the Brazilian Society of Cardiology for the management of heart failure and ventricular dysfunction induced by anthracyclines. chemo: chemotherapy; HF: heart failure; LVEF: left ventricular ejection fraction.*

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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