Review Article

Pharmacological Primary Prevention of Chemotherapy-Induced Cardiomyopathy: What is the Best Approach?

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Introduction

Advances in oncology, such as better access to health care system, earlier cancer diagnosis, and new chemotherapies, have led to longer survival of oncologic patients over the last decades.[1] However, this population is vulnerable to cardiovascular drug-related adverse events like cardiomyopathy, which leads to heart failure and impairs survival and quality of life.[2,3] Among different classes of chemotherapeutic agents, anthracyclines (ANT) stand out as the most related to cardiomyopathy, which may affect cancer survivors in 9% of all cases.[4]

The most widely recognized definition of cardiotoxicity is based on changes in left ventricular ejection fraction (LVEF).[5] A decline of 10% to a value below 50% or a decline associated with heart failure symptoms during or after the use of a cardiotoxic agent suggests cardiotoxicity.[2]

Once chemotherapy-induced cardiomyopathy is present, prompt heart failure treatment should be started with neurohormonal antagonists, such as angiotensin converting enzyme inhibitor (ACEI), angiotensin receptor blockers (ARB), and betablockers. Despite contemporary heart failure treatment, up to 89% of patients with ANT-induced cardiotoxicity do not experience complete recovery.[6,7] 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.

Monitorization of cardiotoxicity

The frequency of cardiovascular evaluation in monitorization of cardiotoxicity depends on both individual cardiovascular risk, which involves individual risk factors, and intrinsic chemotherapy risk. The following are known risk factors for cardiotoxicity: female sex; age below 18 years or over 65 years; comorbidities like systemic arterial hypertension or other previous cardiovascular disease, diabetes, obesity, or renal insufficiency; high ANT cumulative dose; chemotherapy association, especially trastuzumab and ANT; genetic alterations such as trisomy 21; hemochromatosis; and mediastinal radiotherapy (Table 1).[8,9] The incidence of cardiovascular events during the 10 days following ANT administration is less than 2% in the low-risk group and more than 5% in the high-risk group, leading to different protocols based on individual risk.[10]

A position paper of the European Society of Cardiology[12] suggests monitorization using echocardiogram (including global longitudinal strain [GLS] and 3D LVEF) and biomarkers in order to identify subclinical markers of cardiotoxicity and consider cardioprotective medications. The frequency of evaluation depends on individual risk considering individual and chemotherapy factors. Figures 1 and 2 show the European Society of Cardiology protocol for ANT and trastuzumab, respectively.

The Brazilian Cardio-oncology guideline[13] suggests a slightly different approach (Figures 3 and 4). Different intervals are also used depending on baseline LVEF. For ANT, 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 ANT. 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%, in addition to 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 first image evaluation should be made after 12 weeks and 18 weeks and at the end of treatment.

Subclinical cardiotoxicity markers

The actual definition of cardiotoxicity, although largely used in different trials, raises some concern, since LVEF reduction may represent a late stage of myocardial injury and, therefore, it only allows diagnosis in 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 elevated biomarkers[14] and myocardial strain reduction[15] as subclinical cardiotoxicity markers, although there is not yet any formal recommendation for treatment based on them.

Troponin is a complex of three regulatory proteins (troponin C, troponin I, and troponin T) that are integral to muscle

Keywords

Cardiotoxicity; Heart Failure; Pharmaceutical Preparations; Primary Prevention.

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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), lipossomal formulations	Age > 18 and < 50 years
Trastuzumab without ANT	
Medium risk of cardiotoxicity	
Modest-dose ANT (doxorubicin 200 to 400 mg/m^2 or epirubicin 300 to 600 mg/m^2)	Age 50 to 64 years 1 to 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 imune 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 Reduced or low-normal LVEF (50% to 54%) pre-treatment Prior cancer therapy
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	
VEGF tyrosine kinase inhibitors following previous ANT chemotherapy	

ANT: anthracycline; Bcr, breakpoint cluster region; 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.[11]

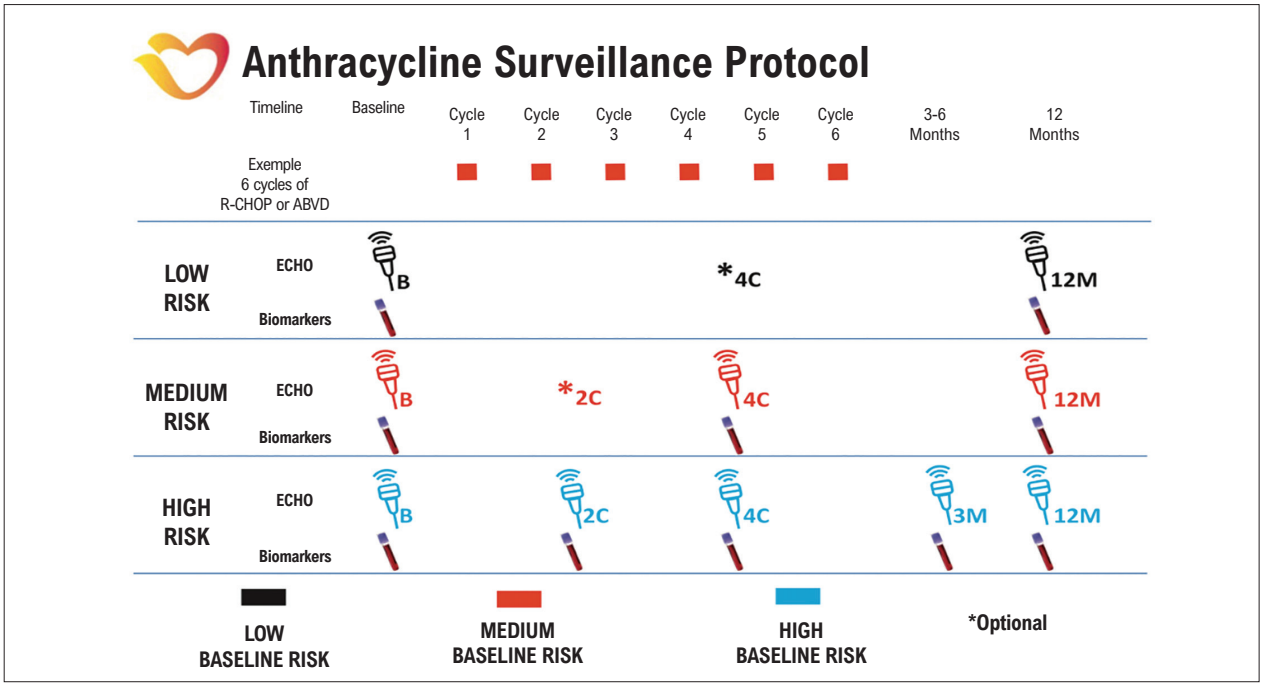

Figure 1 – *A surveillance pathway using biomarkers and echocardiography for cancer patients receiving six cycles of anthracycline chemotherapy with timing based upon baseline cardiovascular risk. Pathways for low risk, medium risk and high risk are presented. ABVD, doxorubicin, bleomycin, vinblastine; B, baseline pre-treatment; C, cycle of chemotherapy; M, months post-final cycle; R-CHOP, Cyclosphosphamide, doxorubicin, vincristine, prednisone with rituximab. *Optional additional assessment timepoints.*

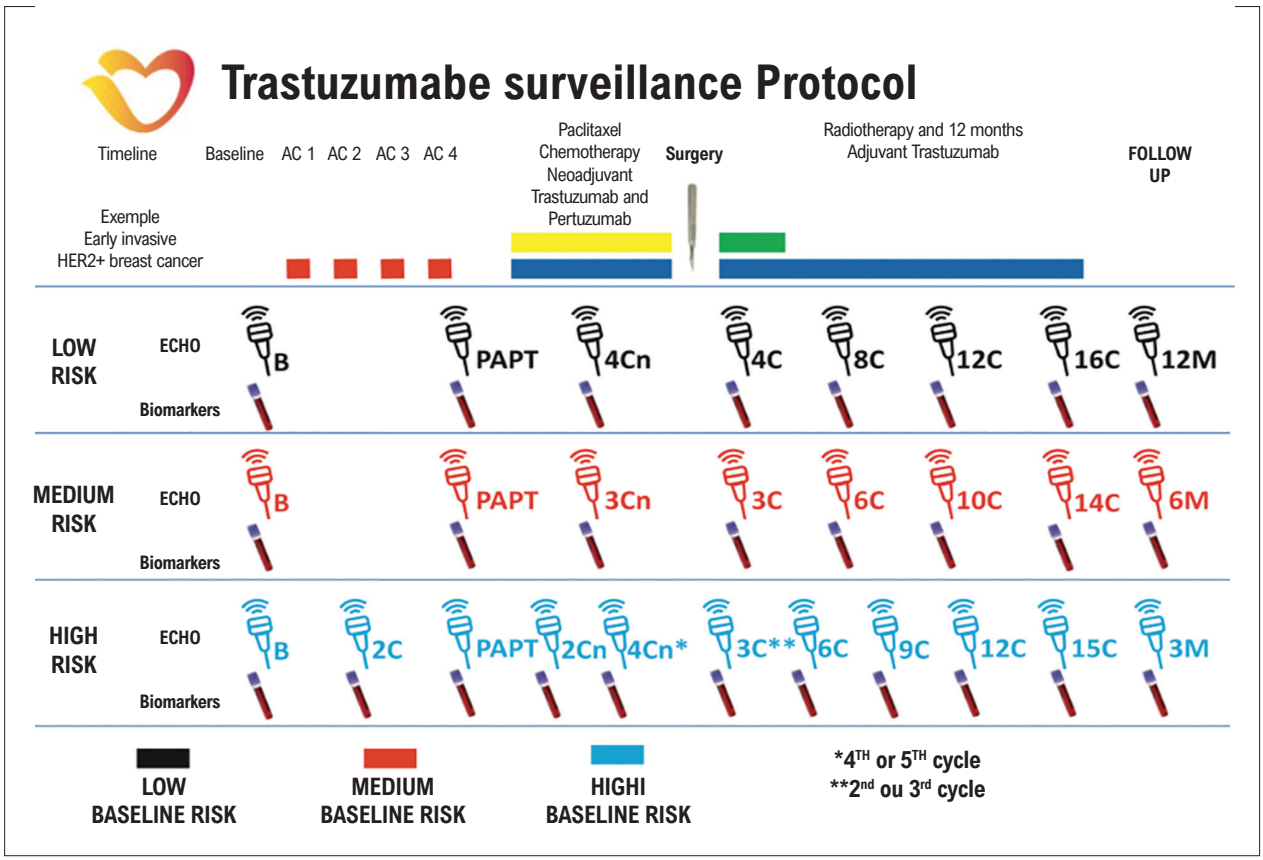

Figure 2 – *A suveveilance pathway using biomarkers and echocardiography for patients receiving neoadjuvant anthracycline (AC) chemotherapy (doxorubicin or epirubicin) and tratuzumab followed by 12 months of adjuvant tratuzumab for HER2+ early breast cancer with timing based upon baseline cardiovascular risk. Pathways for low risk, medium risk and high risk are presented. B, baseline pre-treatment; C, Chemotherapy or adjuvant trastuzumab; Cn, neoadjuvant cycle of tratuzubab; M, months post-fina cycle; PAPT, post-anthracycline chemotherapy pre-trastuzumab. *, **Optional additional assessment timepoints.*

contraction in skeletal muscle and cardiac muscle. Prolonged ischemia, trauma, inflammation, or cardiotoxic agents may result in injury of cardiac cells. This injury is accompanied by the destruction of cell membranes and organelles and the release of troponin and other proteins into the blood.[16] These proteins are the most studied biomarker in subclinical ANT-induced cardiotoxicity.[14]

Cardiac troponin I (cTnI) elevation was described in one third of patients after high-dose ANT,[15,17] and the degree of cTnI elevation was associated with the cumulative dose of ANT.[18] This biomarker is also associated with the degree of left ventricular dysfunction. In one cohort, patients with 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.[19] In another study, cTnI values persisting > 0.08 ng/mL over a month after therapy were associated with 84% risk of cardiotoxicity, while cTnI below the reference range was associated with 1% risk.[17]

In addition to troponins, other biomarkers have been studied in subclinical cardiotoxicity. Natriuretic peptides have controversial correlation with cardiotoxicity in the literature. Some evidence suggests an association between NT-proBNP level and cumulative dose of ANT.[20,21] However, in two cohorts, while troponin predicted cardiac toxicity, natriuretic peptides did not.[22,23] Markers of inflammation and endothelial dysfunction are also targets of research,[14] 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 study of global and regional myocardial deformation to detect subtle alterations in systolic function, particularly related to ANT chemotherapy.[24] Evidence including a metanalysis of 21 studies and 1782 patients with cancer suggests that GLS can identify subclinical myocardial dysfunction, and it also has prognostic implication regarding chemotherapy-induced cardiotoxicity or heart failure.[15] The use of GLS could identify patients with higher risk of cardiotoxicity and improve cardiac surveillance.

Following this rationale, the SUCCOUR Trial evaluated a GLS-based-approach to initiation of cardioprotection compared to standard care, to reduce the risk of future LVEF reduction, interruption of cancer therapy or cancer therapy-related cardiac dysfunction.[25] ANT-exposed patients with another risk factor for heart failure were enrolled to start cardioprotection with ACEI and betablocker after 10% reduction in LVEF to less than 55% or 5% reduction with

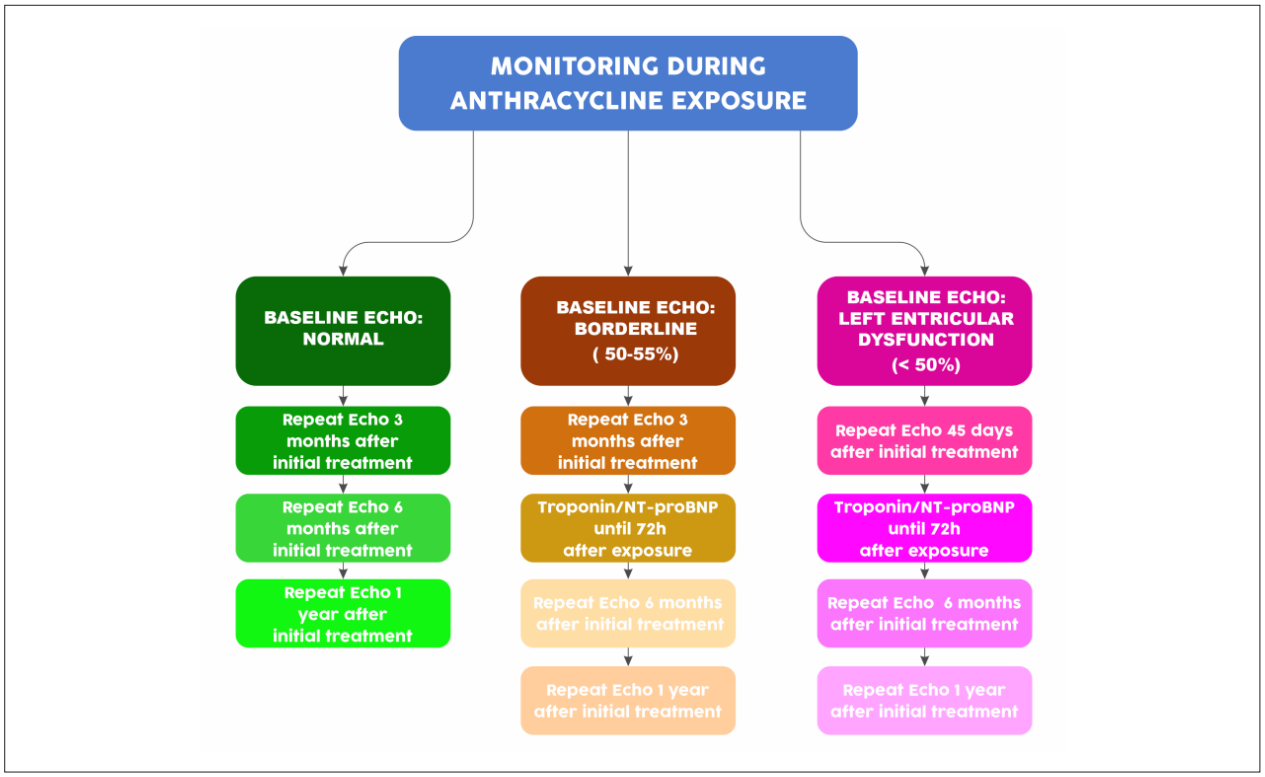

Figure 3 – *Echocardiographic monitoring and analysis of biomarkers in patients using anthracyclines suggested by the Brazilian Society of Cardiology.13 Echo: echocardiogram; NT-proBNP: N-terminal pro-B-type natriuretic peptide; QT: chemotherapy.*

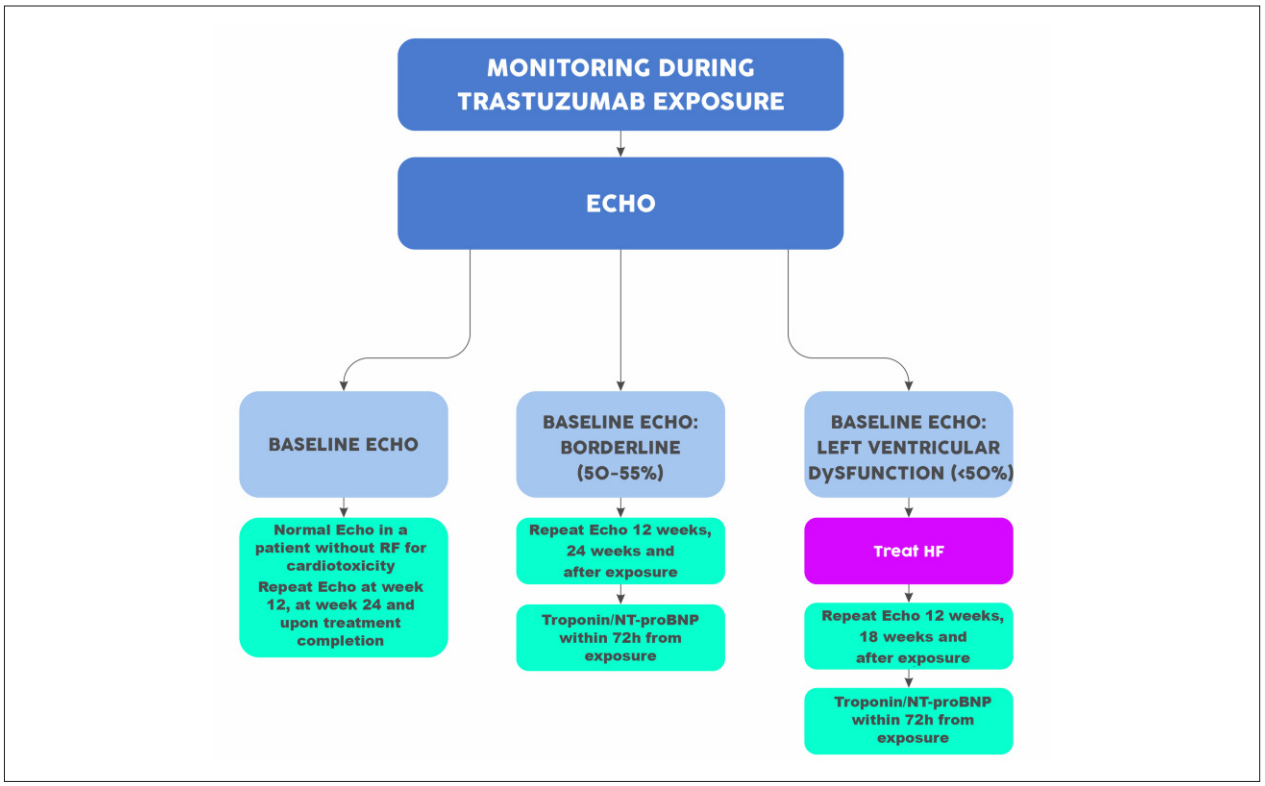

Figure 4 – *Echocardiographic monitoring and analysis of biomarkers in patients using anti-HER2 drugs suggested by the Brazilian Society of Cardiology.[13] Echo: echocardiogram; HF: heart failure; NT-proBNP: N-terminal pro-B-type natriuretic peptide; RF: risk factors.*

symptoms of heart failure or after 12% relative reduction in GLS. 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 in the ejection fraction-guided arm. As a result, 21 patients (13.7%) in the ejection fraction-guided arm compared to 9 patients (5.8%) in the GLS-guided arm met criteria for cancer therapy-related cardiac dysfunction ($p = 0.022$), with a number needed to treat of 13. In a post-hoc analysis, the study also showed lower reduction in LVEF among GLS-guided patients (2.9%) compared to ejection fraction-guided patients (9.1%).

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.[26] It is also important to control weight, treat comorbidities, and, if possible, minimize cardiac radiation. Regarding pharmacological therapy, there are two approaches to primary prevention of ANT-induced cardiotoxicity: reducing the cardiotoxic effects of ANT and initiating a cardioprotective medication.

The first approach is made possible by decreasing cumulative dose of the agent (< 360 mg/m^2 of doxorubicin or equivalent dose of ANT analogues), using continuous infusion and giving preference to liposomal forms of the drug.[27] Preference should also be given to less cardiotoxic ANT analogues, such as epirubicin, idarubicin, and mitoxantrone.

In the second approach, cardioprotective medications are initiated with the aim of reducing myocardial injury. So far, only dexrazoxane has been approved by the United States Food and Drug Administration to avoid ANT cardiotoxicity in metastatic breast cancer patients who received > 300 mg/m^2 of doxorubicin.[28] Dexrazoxane is an iron chelator that changes topoisomerase 2β configuration, preventing ANT interaction and thus preventing its cardiotoxic effect. Different trials showed reduction of cardiovascular events and of the incidence of heart failure among breast cancer patients, 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 ANT exposure. Furthermore, the rate of a partial or complete oncological response, overall survival, and progression-free survival were not affected by dexrazoxane.[29]

Cardiovascular drugs, such as beta-blockers, ACEI, and BRA, showed controversial results and are not recommended as a routine in patients under chemotherapy.[30] Earlier small randomized studies suggested that carvedilol[31] and nebivolol[32] were protective against LVEF changes. In one of the first randomized clinical trials comparing placebo versus carvedilol in patients treated with high doses of ANT chemotherapy, Kalay et al.[31] found a higher reduction in LVEF in the placebo group (69% to 53%) than in carvedilol (70% to 69%) ($p < 0.001$). Differently, the PRADA Trial (Prevention of Cardiac Dysfunction during Adjuvant Breast Cancer Therapy)[33] 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[34] 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 difference was found in the metoprolol group, and there was no difference in cardiac troponins between groups.

Cardinale et al studied cardioprotection using enalapril, an ACEI widely used in the management of heart failure, in 114 patients who developed positive troponin during ANT treatment compared to placebo.[35] The enalapril group had significantly lower incidence of heart failure and asymptomatic ventricular dysfunction. The same author evaluated 273 patients that received enalapril as primary prevention compared to enalapril only in patients who developed positive troponin during chemotherapy.[36] 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),[37] included 200 patients with breast cancer and use of ANT, 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 the results. Interestingly, in this study, patients in the carvedilol arm had lower troponin values than in the placebo arm, raising the possibility of subclinical cardiotoxicity protection. Table 2 shows the main trials evaluating cardioprotective medications in primary prevention.

When to start cardioprotective medications?

Current guidelines recommend assessment of cardiac toxicity using LVEF measurement. If, during treatment, a patient presents LVEF < 50%, cardioprotective medications should be started.[11,12] If LVEF drops below 40%, in addition to cardioprotective medications, antineoplastic treatment should be suspended temporarily based on discussion with the cardiologist and the oncologist (Figures 5 and 6). However, if the patient develops a GLS reduction (absolute ≥ 5% or relative ≥ 15%) or troponin elevation, there is, to date, no formal recommendation for suspension of chemotherapy agents, and cardioprotective medications may be considered.[12]

Conclusion

Regarding pharmacological cardioprotection, current evidence suggests that cardiovascular medications in all patients without stratification do not result in clinical benefit. However, an effort to identify subclinical myocardial damage should be made in order to recognize the subgroup that could benefit from intensive surveillance and cardioprotective medications. More sensitive and reproducible biomarkers such as troponin should be studied in association with GLS to precociously treat

Table 2 – Summary of the most important clinical trials in primary prevention of cardiotoxicity.

Study	Patients	Chemotherapy regimen	Cardioprotective drug	Primary outcome	Follow-up (months)
Cardinale[35] 2006	114	Epirubicin Idarubicin Daunorubicin	Enalapril	Cardiotoxicity incidence: Control: 43% Enalapril: 0% p < 0.001	12
Kalay[31] 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[38] 2010	125	Doxorubicin	Metoprolol Enalapril	No change in LVEF	12
Bosch[39] 2013	201	Idarubicin Daunorubicin	Carvedilol Enalapril	Mean change in LVEF reduction (%) Control: 3.1; p = 0.035 Enalapril + carvedilol: 0.17%; p = ns	6
Kaya[40] 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[33] 2016	126	Epirubicin	Metoprolol Candesartan	Mean change in LVEF reduction (%) Placebo: 2.6 Candesartan: 0.8; p = 0.026 Metoprolol: 1.6%; p = ns	6
Pituskin[41] 2017	94	Trastuzumab	Bisoprolol Perindopril	No change in LVEF	12
Avila[37] 2018	200	Doxorubicin	Carvedilol	No change in LVEF	6
Guglin[42] 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.

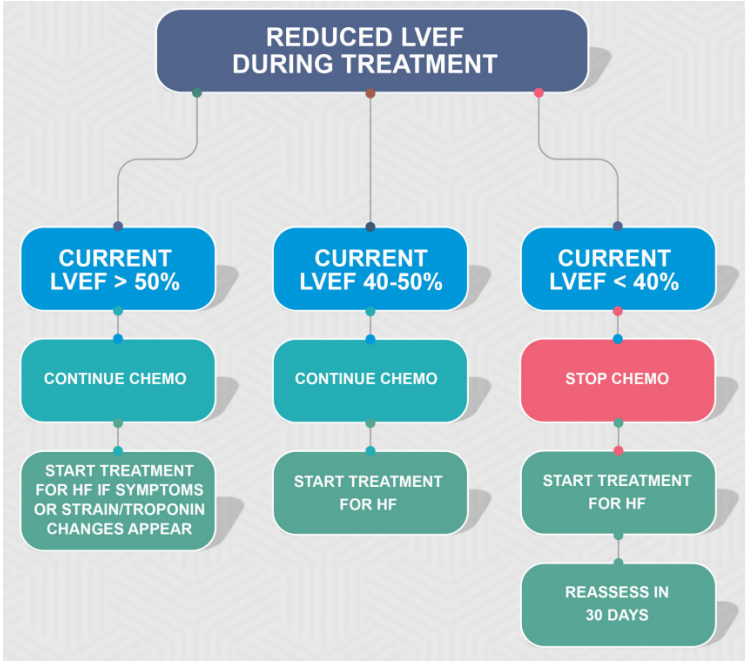

Figure 5 – *Flowchart of the Brazilian Society of Cardiology for the management of heart failure and ventricular dysfunction induced by anthracyclines. chemo: chemotherapy; HF: heart failure; LVEF: left ventricular ejection fraction.*

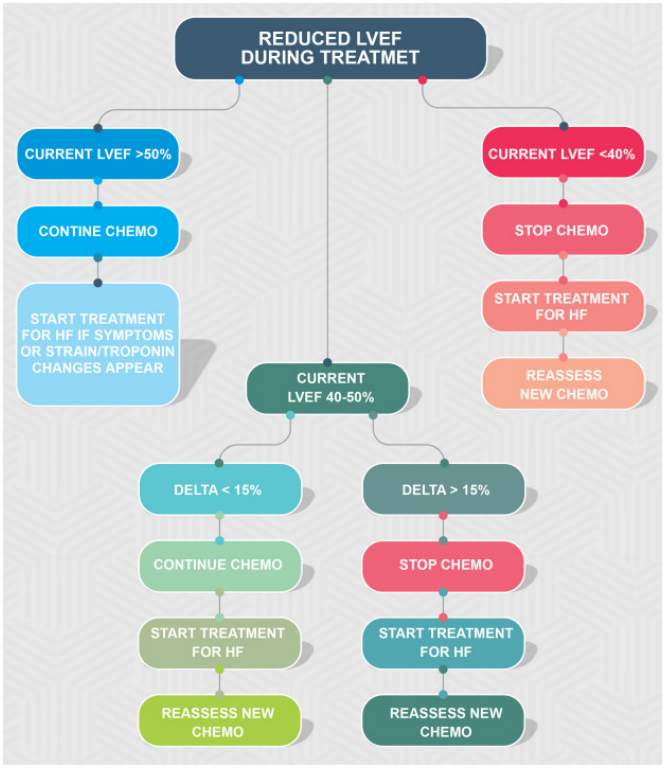

Figure 6 – *Flowchart of the Brazilian Society of Cardiology[13] for the management of heart failure and ventricular dysfunction induced by anti-HER2 therapy. chemo: chemotherapy; HF: heart failure; LVEF: left ventricular ejection fraction.*

cardiovascular dysfunction related to chemotherapy and reduce morbidity and mortality in this population.

Author Contributions

Conception and design of the research, Acquisition of data, Analysis and interpretation of the data, Writing of the manuscript, Critical revision of the manuscript for intellectual content: Avila MS, Belfort DSP, Wanderley Júnior MRB.

Potential Conflict of Interest

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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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