

The prevalence of breast cancer in women is a fundamental problem in public health worldwide. There is consensual evidence that many chemotherapeutic agents might have harmful effects on the cardiovascular system of patients. The cardiotoxicity of chemotherapeutic drugs might lead to ventricular systolic dysfunction and heart failure, and consequently cardioactive drugs, such as antihypertensive, might mitigate those cardiac dysfunctions. Thus, this study carried out an integrative literature review on the potential benefits of cardioactive drugs in cardiovascular repercussions resulting from chemotherapy (CT), especially in women with breast cancer. The research involved articles available on the PubMed, LILACS, and MedLine databases, using as descriptors “breast cancer”, “chemotherapy”, “cardiotoxicity”, and “antihypertensive”; 11 articles were selected. The data corroborate an association between the use of antineoplastic drugs (anthracyclines, fluorouracil, and anti-HER2 monoclonal antibody, trastuzumab) and cardiotoxic effects, and anthracyclines are the most studied CT drugs in relation to cardiac dysfunction. The cardioprotective effect of cardioactive drugs, including non-selective and selective beta-blockers classes, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers, could be observed in clinical outcomes. Nonetheless, the drugs have different cardioprotective effects on breast cancer patients and left ventricular ejection fraction; the serum concentrations of troponins and brain natriuretic peptide were the most frequent parameters analysed in selected articles. In summary, cardiovascular parameters should be followed-up in patients undergoing oncology treatment in all stages, regardless of the therapeutic scheme carried out, given the risk of developing and worsening such heart conditions.

Key words: breast neoplasms, antineoplastic agents, cardiotoxicity, cardioactive drugs, antihypertensive agents.

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Heart protective effects of cardioactive drugs associated with antineoplastic treatment against breast cancer

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Introduction

The increased estimation of new cases of cancer worldwide has been followed by improvements in early diagnosis and treatment, leading to an enhancement of cancer survivors. Breast cancer is the most common malignant neoplasm in women worldwide, and there will be about 2.1 million new cases of this cancer in the year 2018 [1]. The risk factors associated with breast cancer development, including tobacco and alcohol abuse, inadequate nutrition, obesity, sedentary behaviour, and diabetes mellitus, are common to other chronic diseases, such as cardiovascular disease and arterial hypertension [2]. In this context, it is recurrent the development of breast cancer in women previously diagnosed with cardiovascular diseases, or even cardiovascular manifestations during or after breast cancer treatment [3].

Breast cancers are highly heterogeneous and can be classified according to the expression of cell hormone receptors, such as oestrogen (ER), progesterone (PR), and human epidermal growth factor receptor type 2 (HER2). Some features of the tumour are crucial for treatment planning, i.e. phenotypic characterization, location, size, invasion, and the presence of metastasis in draining lymph nodes and/or distant tissues [4]. In addition, several aspects related to the patient might be considered for treatment planning, such as age, comorbidities, exposure to risk factors, previous health conditions, profile regarding menopause and hormone replacement, and family history of breast and ovarian cancer [5]. Thus, the treatment planning should consider the classification of breast tumour stages, which can be grouped into local treatment, such as surgery and radiotherapy, and systemic treatment, which includes chemotherapy (CT), and hormone and biological therapy, according to the American Joint Committee on Cancer protocols [6].

Chemotherapy, nonetheless, is the modality of treatment whose duration can be longer, considering that it can be instituted in different arrangements of drug combinations, in accordance with the proposed therapeutic plan. A combination of anthracyclines, taxanes, antimetabolites (5-fluorouracil or capecitabine), cyclophosphamide, or carboplatin is usually applied in adjuvant or neoadjuvant CT regimes [5]. Despite its safety, CT has been associated with cardiotoxic effects of these drugs, and it has been described as the aggravating factor for comorbidities, especially in women who already have a cardiovascular disease [7]. Anthracyclines have been associated with cardiac dysfunctions, and those conditions might be increased if anti-HER-2 monoclonal antibodies and radiotherapy regimes are combined, particularly when the thoracic area is exposed to more than 30 Gy [8].

The cardiotoxicity of chemotherapeutic drugs can manifest itself in an acute, subacute, or chronic form, with emphasis on myocardial injury with ventricular systolic dysfunction and heart failure, whose frequency and severity has frequently been reported [9]. There is consensual data towards

the mutual association between cardiac changes and vascular hypertension, a multifactorial clinical condition characterized by sustained elevation of blood pressure levels ≥ 140 and/or 90 mmHg. Thus, we carried out an integrative literature review on the potential benefits of cardioactive drugs in cardiovascular repercussions resulting from CT in women with breast cancer.

Material and methods

A bibliographic survey was carried out, including articles available in the PubMed, LILACS, and MedLine databases through research with the descriptors “breast cancer”, “chemotherapy”, “cardiotoxicity”, and “antihypertensive”. The criteria for selecting the articles were determined by the type of methodological design (clinical trials, meta-analysis, systematic reviews, and randomized studies) published in English language in the period 2010–2021. We excluded repeated articles or those with content not available in full text. The search generated 20 articles, of which 7 were found in duplicate, one paper was not in the proposed language, and 3 were not available in full text. Finally, 11 articles were analysed in this review. The methodological quality of the articles used was assessed according to the Consolidated Standards of Reporting Trials 2010 (CONSORT) criteria, assigning a score of 0 (does not meet) or 1 (meets) for each of the 25 criteria. The average value of the index for the selected articles was 20.72 ± 2.10 .

Results

The included articles and the information from these manuscripts are summarized in Table 1. The data obtained in the selected studies analysed the interaction between antineoplastic drugs (anthracyclines, fluorouracil, and anti-HER2 monoclonal antibody, trastuzumab) and cardioactive drugs, such as non-selective and selective beta-blockers (β -B) classes, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARB). The main clinical outcomes analysed were left ventricular ejection fraction (LVEF), and the serum concentrations of troponins or brain natriuretic peptide (BNP) (Table 1).

The interactive effect in the simultaneous use of anthracyclines and β -B was evaluated in 192 breast cancer patients under CT with cyclophosphamide and doxorubicin (total cumulative dose of 240 mg/m^2), and paclitaxel, in a prospective, double-blind, placebo-controlled study. In 6 months of evaluation, a 10% reduction in LVEF was observed in 14.0% of patients under treatment ($n = 27$), with no differences between the placebo groups or those using β -B. Troponin I (TnI) and BNP levels increased since the beginning of CT in both groups, but TnI levels were statistically lower in patients using carvedilol ($p < 0.05$). Furthermore, the incidence of diastolic dysfunction, systolic and diastolic BP levels, and heart rate were lower in patients using β -B [10].

Additionally, the cardiotoxic effects measured by echocardiogram (ECHO) before and after CT showed that the group treated with β -B ($n = 30$) was able to control cardiac changes, while in the placebo group ($n = 40$) there was a significant decrease in all parameters and cardiac strain

rates ($p < 0.001$) [11]. Similar results were also found when another β -B (nebivolol) was evaluated in patients undergoing therapy with anthracycline (epirubicin) for a period of 6 months [12]. In that study, the ECHO parameters of end-systolic and end-diastolic diameters of the left ventricle increased significantly in the placebo group. The group that used the β -B did not show changes in morphological parameters on the ECHO, but the LVEF and the myocardial performance index remained stable in the group that used this drug ($p > 0.05$) [12].

The cardioprotective effect of ACE inhibitors (enalapril) was evaluated in patients undergoing CT with anthracyclines (epirubicin and doxorubicin) in a multicentre, randomized, double-blind study (International CardioOncology Society-one – ICOS-ONE) [13]. Patients were randomly allocated to a group that used preventive ACE inhibitors, while the control group used the drug only when there was an increase in troponin levels (a parameter that was evaluated quarterly for one year after the last CT cycle). There were no differences between the groups regarding the proportion of patients with elevated troponin levels or the period for the first troponin elevation. The incidence of cardiac events was very low in both groups, and the average LVEF during follow-up was similar to baseline values between the study groups, with a 10% reduction in LVEF in only 3 patients [13]. Thus, the results show that the ACE inhibitor does not seem to prevent the occurrence of cardiotoxicity, but it was able to prevent the progression of previous existing cardiac changes. Otherwise, the synergic effect of ACE inhibitors (lisinopril) and β -B (bisoprolol) preserved the LVEF after 6 cycles of CT regimes using anthracyclines [14].

The synergistic effects between ARB (candesartan) and β -B (metoprolol) in the control of cardiotoxic effects induced by adjuvant CT regimen with a combination of anthracycline, 5-fluorouracil, and cyclophosphamide were also evaluated [15]. In this randomized, placebo-controlled, double-blind study, the combined effect of ARB and β -B was evaluated in a population that did not have severe concomitant disease, previous cardiovascular disease, and neither indications nor contraindications for cardioactive drugs ($n = 20$). Patients were randomly assigned to homogeneous groups to receive one of the following treatment combinations: ARB- β -B, ARB-placebo, β -B-placebo, or placebo-placebo. Angiotensin receptor blockers (candesartan) prevented the decline of LVEF compared to the placebo group, and ARB did not interfere with the right ventricular ejection fraction parameters, the left ventricular global longitudinal strain, the ratio between the diastolic velocity (E) of the mitral flow and the diastolic velocity (E/E'), cardiac TnI, and BNP levels. Moreover, it was observed that the decline in LVEF was similar among the participants allocated to the β -B (metoprolol) and placebo groups. The isolated use of ARB (ARB-placebo group) showed better control of the reduction in LVEF levels compared to the simultaneous use of ARB- β -B or placebo. No significant difference was observed between the placebo-placebo group and the β -B-placebo group [15]. These authors also performed a clinical trial and analysed the interaction between β -B, ARB, and chemotherapeutic drugs evaluated in a homoge-

Table 1. Summary of articles relating to cardiotoxicity associated with the use of chemotherapy and cardioactive drugs

Author(s) (year), reference, CONSORT	Sample	Type of study	Aim of the study	Results
Avila <i>et al.</i> , 2018 [10] Consort – 22	192	Prospective, double-blind, randomized, placebo-controlled study	To evaluate the role of β -B (carvedilol) in the prevention of cardiotoxicity in CT with anthracyclines	Incidence of cardiotoxicity 13.5–14.5% after CT. Use of β -B did not prevent early onset of LVEF reduction. The use of β -B is associated with reduced levels of troponin and diastolic dysfunction
Behesti <i>et al.</i> , 2016 [11] Consort – 16	70	Double-blind, randomized, placebo-controlled study	To evaluate the preventive effect of β -B (carvedilol) on CT-induced cardiotoxicity with anthracyclines (doxorubicin)	β -B (carvedilol) prevented doxorubicin-induced cardiotoxicity
Kaya <i>et al.</i> , 2012 [12] Consort – 21	45	Prospective and double-blind study	To evaluate the effect of prophylactic use of β -B (nebivolol) in the prevention of anthracycline-induced cardiotoxicity in patients with breast cancer	The prophylactic use of treatment with β -B (nebivolol) protected the myocardium against anthracycline-induced cardiotoxicity
Cardinale <i>et al.</i> , 2018 [13] Consort – 20	273	Randomized, controlled study	To analyse prophylactic use of ACEI (enalapril) before CT in all patients; can prevent the increase in troponin and prevent left ventricular dysfunction	The prophylactic use of ACE inhibitors did not alter clinical outcomes. However, it showed benefit in the progression of LV dysfunction
Wihandono <i>et al.</i> , 2021 [14] Consort – 22	74	Randomized, placebo-controlled study	To examine the benefits of adding ACEI (lisinopril) and β -B (bisoprolol) to reduce the cardiotoxicity of breast cancer patients receiving anthracycline CT	There was a significant difference in the change in LVEF between the control arm and the treatment arm with the combination of ACE inhibitors (lisinopril) and BB (bisoprolol). This can prevent cardiotoxicity in patients with locally advanced breast carcinoma, who have received anthracycline CT
Gulati <i>et al.</i> , 2016 [15] Consort – 23	120	Double-blind, randomized, placebo-controlled study	To evaluate the combined use of ARB (candesartan) and β -B (metoprolol) in preventing LVEF decline in CT with anthracycline, associated with trastuzumab and radiation	The use of ARB provides protection against early decline in global left ventricular function. Use of β -B alone or combined with ARB was not superior to the use of ARB-placebo
Heck <i>et al.</i> , 2018 [16] Consort – 21	69	Double-blind, randomized, placebo-controlled study	To evaluate the combined use of ARB (candesartan) and β -B (metoprolol) to prevent cardiac damage after CT with anthracycline	β -B has a protective effect against anthracycline-induced cardiotoxicity. The use of ARB did not interfere with the total myocardial cell volume. The combined use of ARB and β -B was no more advantageous than the isolated use of these drugs
Lee <i>et al.</i> , 2021 [17] Consort – 23	195	Randomized and placebo-controlled study	To determine whether early detection of subclinical cardiotoxicity with preventive administration of low-dose ARBs or β -B will mitigate the decrease in LV systolic function in patients with breast cancer without CV risk	Administration of low-dose candesartan in patients treated with doxorubicin-containing CT has been shown to be effective in preventing early decrease in LVEF in patients with breast cancer without CV risk
Boekhout <i>et al.</i> , 2016 [18] Consort – 19	210	Randomized and placebo-controlled study	To evaluate the cardioprotective effect of ARB (candesartan) in CT with anthracycline, associated with trastuzumab	Concomitant use of ARB does not protect against a decrease in LVEF during or shortly after treatment with anthracyclines and trastuzumab
Guglin <i>et al.</i> , 2019 [19] Consort – 19	468	Prospective, double-blind, randomized, placebo-controlled study	To evaluate the cardioprotective effect of ACEI (lisinopril) or β -B (carvedilol) in CT with anthracycline, associated with trastuzumab	In patients with HER2-positive breast cancer treated with anthracyclines, the use of lisinopril or carvedilol should be considered to minimize interruptions in treatment with trastuzumab, due to a reduction in LVEF
Pituskin <i>et al.</i> , 2017 [20] Consort – 22	94	Double-blind placebo-controlled study	To evaluate the action of ACEI (perindopril) and β -B (bisoprolol) in the prevention of cardiotoxicity in CT with anthracycline, associated with trastuzumab	ACEI and β -B protected against LVEF declines, but left ventricular remodelling was not prevented by these drugs

ACEI – angiotensin-converting enzyme inhibitor, ARB – angiotensin receptor blocker, β -B – beta-blocker, CT – chemotherapy, HER2 – human epidermal growth factor receptor type 2, LVEF – left ventricular ejection fraction

neous population of 120 women with breast cancer [16]. Women with symptomatic chronic heart failure (HF), heart valve disease, coronary heart disease, or arrhythmias were excluded from the sample, while patients included in the study were examined by cardiovascular magnetic resonance at the beginning and at the end of the final CT cycle with anthracycline, 5-fluorouracil, and cyclophosphamide. The same image diagnosis procedure was carried out when additional radiotherapy, taxanes, or trastuzumab therapy was performed. Participants were divided into 4 experimental groups to use combined pairs of ARB (candesartan), β -B (metoprolol), or placebo. Chemotherapy regimens with high doses of anthracycline were associated with significant increases in the extracellular volume fraction and in the total myocardial cell volume. Furthermore, during therapy with anthracycline, LVEF decreased by 3.1% ($p < 0.01$) in the placebo-placebo group, but there was no change in the myocardial extracellular volume fraction in patients who had not received ARB. However, in patients who received ARB, the total cell volume decreased significantly when compared to other participants. Beta-blockers did not affect LVEF parameters, myocardial extracellular volume fraction, total myocardial cell volume, or total cell volume [16]. More recently, a prospective clinical trial demonstrated the protective effects of ARB (candesartan) compared with β -B (carvedilol) in women with low cardiovascular risks [17]. For those patients, pretreatment with low-dose candesartan reversed the LVEF after 12 months of CT regimes with anthracyclines [17].

The cardioprotective effects of ARB (candesartan) in patients using anti-HER-2 monoclonal antibody (trastuzumab) and anthracyclines were evaluated in a randomized placebo-controlled clinical trial [18]. In that study, after treatment with trastuzumab, 13 of 103 enrolled patients developed symptomatic HF on mild exertion (NYHA class II or higher) in the placebo group, in comparison with 8 patients treated with ARB. Participants using ARB or placebo had similar BNP and troponin levels, as well as LVEF values. Therefore, the results of the trial do not support the hypothesis that the concomitant use of ARB and trastuzumab, in the initial stages of breast cancer after treatment with anthracyclines, prevents or controls the development of cardiotoxic effects related to immunotherapy [18]. Otherwise, clinical and biomarker parameters should be considered in the interpretation of clinical trials results. Data from clinical trials indicated that ACE inhibitors (lisinopril) and β -B (carvedilol) did not change the parameters of cardiotoxicity in women with HER2-positive breast cancer (in initial stages), who used trastuzumab after CT regimen with anthracyclines ($n = 189$) or without this CT ($n = 279$) [19]. However, despite global health status values and BNP levels being similar between the analysed groups, β -B seems to prevent cardiotoxic effects with a better performance than ACE inhibitors, according to the risk indexes for the development of cardiotoxicity (0.49 for β -B, $p < 0.01$; and 0.53 for ACE inhibitors, $p < 0.05$) [19]. Thus, the analysis of cardiotoxicity-free survival in the anthracycline cohort showed that both β -B and ACE inhibitors were protective compared to placebo.

The protective performance of β -B was similar to that of patients under immunotherapy with anti-HER-2 monoclonal antibodies, without previous cardiovascular risk factors [20]. In this placebo-controlled study ($n = 30$), the cardioprotective effects of ACE inhibitors (perindopril, $n = 33$) and selective β -B (bisoprolol, $n = 31$) were evaluated in patients under a CT regimen with docetaxel, carboplatin, and trastuzumab. After completion of therapy with trastuzumab, the mean changes in the LV end-systolic and diastolic volume index were similar between the groups. However, the absolute mean change of LVEF was lower in the group treated with β -B compared to placebo or to the group treated with ACE inhibitors at the end of therapy. Nonetheless, interruptions in trastuzumab therapy, due to a 10-percentage point drop in LVEF, were lower within the groups treated with ACE inhibitors (3 out of 33 patients) and with β -B (3 out of 31 patients) compared to placebo (9 of 30 patients; $p < 0.05$) [20].

Discussion

This study aimed to carry out an integrative literature review of the potential benefits of cardioactive drugs in cardiovascular repercussions resulting from CT in women with breast cancer. For this group of patients, hormonal modulation and radiotherapy might increase the cardiotoxicity in breast cancer [21]. However, cardiotoxicity induced by CT, even in patients with a low cardiovascular risk, is an emerging keypoint in oncology. It is necessary to consider that cardiac complications may imply the interruption of the CT treatment, given that HF presents a prognosis as poor as that of many neoplasms, which will compromise the follow-up of the patient undergoing oncologic treatment [22].

Thus, the evidence presented in the selected studies of this review demonstrates that CT treatment is associated with cardiovascular dysfunction [22], even in patients who do not present cardiac changes at the beginning of treatment [9, 15, 16, 20]. Regarding the drugs commonly used in breast cancer CT, anthracyclines, such as doxorubicin and epirubicin, present cardiotoxic effects associated with ventricular dysfunction and HF, which is the main cause of mortality in cancer survivors [9]. These effects are dose-dependent, and some strategies, such as prolonged duration of infusion administration, dose fractionation, and use of liposomal formulations, might minimize adverse effects [4]. In addition, a clinical approach that might control the LVEF after anthracycline regimens of CT is the use of cardioactive agents; nonetheless, those drugs present different cardioprotective effects for oncology patients. Less heart damage was observed after combined use of ARB and β -B in patients taking high doses of anthracyclines, but the concomitant use of other CT drugs can interfere with clinical outcomes [23]. According to a recent cardio-oncology guideline (2020), the use of the β -B, ACE, and ARB classes is recommended for the prevention and treatment of cardiac toxicities associated with CT [9, 24]. Moreover, the β -B showed positive effects by reducing serum levels of biomarkers and maintaining LVEF when associated with low-dose anthracycline. However, while

ACE inhibitors did not prevent cardiotoxicity, they prevented its progression. Thus, it is still controversial whether the prophylactic use of cardioactive drugs could mitigate cardiovascular complications induced by CT, given the inconsistencies between clinical data and laboratory tests [10, 13, 15, 18].

From the data analysed in this review, the LVEF and the serum concentrations of troponins or BNP were the main clinical parameters analysed in those clinical trials (Table 1). Anthracyclines are associated with DNA damage, leading to impaired function of topoisomerases II, production of reactive ionic species, and release of histone [25]. Also, in cardiomyocytes, oxidative stress induced by those drugs and membrane damage, via lipid peroxidation, might be associated with the cardiotoxicity. In addition, anthracyclines interfere with Ca^{2+} uptake through adrenergic and adenylate cyclase dysfunction, and this mechanism can contribute to cardiac muscle necrosis [23, 26, 27]. In this context, BNP has demonstrated an important role as a biomarker associated with the risk of developing cardiovascular disease after anthracycline CT [28, 29]. Concerning troponins, cumulative data demonstrate that this biomarker is released from cardiomyocytes after anthracycline administration [29]. In addition, there are 2 isoforms of cardiac troponins (cTn I and T) which play a controversial role as biomarkers of cardiac dysfunction, considering that cTnT does not show a direct association with myocardial infarction and coronary heart disease [30]. The analysis of troponin and BNP levels was in agreement with clinical findings, and the elevation of these biomarkers can be used as a cardiotoxicity assessment method in clinical practice [31, 32]. In addition, non-invasive cardiac imaging tests, such as ECHO and magnetic resonance imaging (MRI), are useful to address the cardiac safety profile of antineoplastic therapy, in an attempt to avoid the potential effects of HF [33]. Magnetic resonance imaging is important for cardiac evaluation with the potential to detect myocardial changes and deterioration of heart function early, but the availability and access to these exams make its application difficult [33].

In view of this evidence, it is necessary that cardiovascular evaluation precedes CT treatment, regardless of the therapeutic strategy to be carried out, especially in patients who already have associated risk factors. Thus, current guidelines recommend the assessment of cardiac function, which can be performed with Doppler ECHO or scintigraphy, in patients whose treatment involves the use of anthracyclines or trastuzumab [34]. The blockage of HER-2 receptors with monoclonal antibodies like trastuzumab interferes not only with breast cancer cells, but also with cardiac cells that highly express this receptor [35]. HER-2 receptor blockade with trastuzumab leads to increased ROS production in human cardiomyocytes and hampered autophagy of these cells, which is an essential mechanism to regulate cell response against stressful stimuli. The use of these immunotherapeutic agents has been associated with an increased risk of heart failure, in a symptomatic or asymptomatic manner, and with a progressive reduction of reversible LVEF after the interruption of drug administration in most cases [34].

It is worth mentioning that CT uses drugs in high concentrations, with a dosage regimen in cycles with intervals of administration that can be 15–21 days, and periodic cardiac evaluations must constitute standard procedures and protocol in oncology treatment units. Even in therapeutic regimens in which drugs are administered in low doses for a longer period, the control of cardiological patterns must be monitored regularly [36]. One of the limitations of the studies is that the clinical parameters analysed in each trial are not homogeneous and differ in terms of laboratory (serum dosage of troponin and BNP) and imaging (ECHO, MRI) exams, characteristics of enrolled population (with or without previous cardiovascular changes), and the follow-up period after the end of CT. Furthermore, considering the complex mechanisms associated with cardiomyocyte dysfunction, and that pathological pathways are not necessarily common to other cardiac diseases [26], some limitations of cardioprotective effects achieved by cardioactive drugs are to be expected [26, 29].

Another limitation of those clinical trials is related to population groups. Most of the studies analysed here were developed in European, North American, and Middle Eastern countries, and for the miscegenated population, with racial groups that present different cardiovascular risks, it is necessary to perform clinical trials adapted to those circumstances [37]. Moreover, the clinical trials must monitor the survival period after cancer treatment, and new prospective studies and cohorts should be performed. According to this evidence, it is important to investigate the possibility of drug interactions between antineoplastic drugs and those used in the management of cardiovascular diseases, especially in view of the possibility of effects still unknown among classes of immunotherapeutic agents, such as monoclonal antibodies, as well as antiresorptive drugs and receptor blockers. In this scenario, recent data also suggest that statins might decrease the risk of cardiotoxicity after anthracycline and/or trastuzumab exposure [38].

Conclusions

Antineoplastic treatment based on the use of anthracyclines and trastuzumab has been associated with cardiotoxicity, especially if used in high doses. The simultaneous use of cardioactive drugs, such as angiotensin receptor blockers, might prevent the cardiotoxicity induced by anthracycline and trastuzumab protocols. Thus, the use of cardioactive drugs should be considered for the prevention and management of cardiovascular changes associated with CT according to the advantages and limitations of these drug classes.

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