A Systematic Review on Cardioprotection Strategies to Prevent Breast Cancer Therapy Cardiotoxicity

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ABSTRACT

Background: Breast cancer is the most prevalent malignancy among women on a global scale, affecting an average of 2.1 million individuals annually. In addition, several studies have shown that it is often treated using chemotherapy drugs and targeted therapy, but these treatment methods have been reported to have side effects on the cardiovascular system. This indicates that there is a need to develop new and effective strategies to prevent the associated side effects. Therefore, this systematic review aims to obtain cardioprotection strategies to prevent cardiotoxicity in breast cancer patients receiving chemotherapy or targeted therapy.

Methods: Data collection was carried out using the online database PubMed with keywords ((cardioprotection) AND (breast cancer therapy) AND (cardiotoxic) OR (Cardiac dysfunction.)) From the initial search, a total of 150 studies were obtained, while articles that did not meet the eligibility criteria were excluded. Furthermore, the articles were reviewed using full-text reading, leading to the inclusion of nineteen in this systematic review.

Results: A total of eleven studies evaluated the effect of cardio-protective drugs on Anthracycline (ANT), and nine assessed Trastuzumab. The results showed that eight studies used Beta-blocker (BB) as cardio-protective strategies, while one, one, three, two, one, one, and one utilized Angiotensin receptor blockers (ARB), ARB + Beta-blocker, ACE-inhibitor (ACE-I) + Beta-blocker, ACE-I/ARB/BB, spironolactone, statin, and Dexrazoxane (DZR), respectively. In large reports, the risk of CTRCD was reduced by the use of a combination of RAAS inhibitors and Beta-blockers. Furthermore, spironolactone, statins, and DZR mitigated the decrease in LVEF compared to the control group in small studies

Conclusions: Based on the results, chemotherapy decreased left ventricular ejection fraction (LVEF) and induced heart failure. Furthermore, the review showed that a combination of renin-angiotensin-aldosterone system (RAAS) inhibitors and Beta-blockers reduced CTRCD. Future studies in larger settings were needed to investigate the efficacy of other strategies, such as statins, Spironolactone, exercise, and DZR.

INTRODUCTION

Breast cancer is widely recognized as the most prevalent malignancy affecting women globally. The condition affects over 2.1 million women annually, making it the leading cause of cancer-related mortalities. According to previous studies, breast cancer has claimed the lives of over 627,000 patients, accounting for 15% of all female cancer-related deaths [1]. Despite significant advancements in early detection and advanced cancer therapies, such as targeted therapy, the number of long-term survivors has been reported to be on an increasing trend. However, these treatments have also been reported to have acute and chronic side effects. Among these, cardiovascular complications stand out as the most common, posing a threat to both the quality of life and the life span of survivors [2].
The use of cancer therapy, including chemotherapy and targeted therapy, has been associated with an elevated risk of cardiotoxicity or CTRCD (Cancer-Therapy Related Cardiac Dysfunction) [3]. Anthracycline (ANT) is a dose-dependent and primary chemotherapeutic agent for the treatment of breast cancer in adjuvant and metastatic conditions. Furthermore, the administration of ANT with a cumulative dose of 400 mg/m2 increases the morbidity of heart failure by 5%, which escalates to 16% at 500 mg/m2, and peaks at 48% at 700 mg/m2. ANT is well known for its irreversible cardiotoxicity effect, necessitating interruptions or cessation of chemotherapy. Several studies have shown that discontinuing its usage can lead to unfavorable cancer prognosis outcomes [4]. Trastuzumab is a HER2-targeted therapy in breast cancer patients with HER2-positive tumors. The treatment has demonstrated its efficacy in increasing survival rates by reducing the risk of recurrence in the adjuvant setting and prolonging survival in metastatic disease. Compared to Anthracycline, which is associated with irreversible cardiomyocyte necrosis, Trastuzumab is known for causing fully or partly reversible cardiotoxicity [5]. The sequential use of ANT and Trastuzumab has been linked to a higher risk for CTRCD. In this context, 7.5% of patients experienced asymptomatic reduction in left ventricle (LV) systolic function, and 2% of sufferers developed symptomatic heart failure [6]. A multicentre cohort study comprising 10,209 breast cancer survivors reported that the five-year incidence of heart failure was 4.5% for patients treated with ANT and Trastuzumab therapy, compared to 0.8% for others treated with only ANT [7].

The occurrence of LV dysfunction, heart failure, or cardiomyopathy can manifest during or after the completion of cancer therapy. Cardiotoxicity is characterized by a reduction in left ventricular ejection fraction (LVEF) by 10% from baseline, leading to an LVEF value falling below the normal range of < 53% [8]. This indicates that cardioprotective management and strategies are needed to minimize the CTRCD. Therefore, this systematic review aims to discuss the efficacy and recommendations of prophylactic cardio-protection.

MATERIAL AND METHODS

Search Strategy

A literature systematic search for journals online was carried out with the keywords ((cardioprotection) AND (breast cancer therapy) AND (cardiotoxic) OR (Cardiac dysfunction.)) and targeted therapy were included. Patients also received drugs that were known to function in the treatment of heart failure. Relevant titles and abstracts were chosen and evaluated using the PRISMA search strategy.

Eligibility criteria were used for inclusion, including i. Randomized controlled trial (RCT) or cohort studies; ii. Breast cancer patients ≥18 years old; iii. Breast cancer therapy with Anthracycline and/or Trastuzumab; iv. Intervention with any form of cardio-protection strategy during breast cancer therapy; v. Studies needed to report the cardiotoxicity outcomes with changes in LVEF; vi. Timing of outcome was anytime; vii. The study was published from 2012–2022. The exclusion criteria included studies written in other than English and full-text access was not available.

Study Selection

A total of two independent reviewers selected the articles, extracted data, and conducted the analysis. Furthermore, potential titles and abstracts were assessed further for full-text evaluation. Any disparities were resolved by consensus between the reviewers. Disagreements between reviewers were settled by consensus or the decision of a third independent reviewer when needed. In this review, any disagreement was resolved by consensus by reaching a common understanding through discussions. The reviewers evaluated the titles and abstracts for all studies using the PRISMA search strategy. References in reviewed and excluded papers were examined to identify studies that were not identified through the primary search strategy. The search was limited to the English language, and a list of potential articles for inclusion in the systematic review was generated through the process.

Data Extraction

Extracted data included details regarding the study name or authors, year of publication, study type, the total number of participants, type of breast cancer chemotherapy, cardioprotection strategy, and description of primary outcomes. Furthermore, the data extraction process was conducted by all authors during the review.

Outcome Definition

The primary outcome was the effect of cardio-protection therapy in preventing cardiotoxicity among breast cancer patients undergoing chemotherapy or targeted therapy. The cardio-protective effect was defined by a reduction in mean LVEF by ≥10% or more from any baseline value, in the intervention group compared to the control group.

Quality Assessment

The quality of each study was assessed using the Cochrane Risk of Bias tool for randomized trials (RoB 2) and the Newcastle-Ottawa Scale (NOS) for cohort and case-control studies. Each RCT was evaluated for random sequence generation, allocation concealment, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other potential sources.
of bias. The result of each judgment could be a “High,” “Low,” or “Some Concerns” risk of bias. For cohort and case-control studies, the selection, comparability, and outcome were evaluated. Each study was then graded as “Good,” “Fair,” or “Poor” quality. Furthermore, it was assessed independently by two reviewers, and disagreements were resolved by consensus through discussions.

RESULTS

A total of 150 articles were identified through the electronic search strategy. Figure 1 shows the resultant PRISMA diagram (Preferred Reporting Items for Systematic Reviews and Meta-Analysis). After the removal of duplicate articles by screening the titles and abstracts, a total of 120 studies were excluded because they did not meet the inclusion criteria. For example, the objects were mice or cell cultures, treated with herbal therapies, the language was in Chinese, and published before the year 2012. The full paper of the remaining 30 studies was retrieved for further evaluation. Among these, 11 studies were excluded, because two reported other types of cancer, one was an ongoing trial, one was only published in Chinese, two did not possess full text, two were study protocol, and two were editorial comments. Therefore, a total of 19 selected publications were included in this systematic review. Decreased heart function caused by the administration of chemotherapy drugs or targeted therapy to breast cancer patients could lead to heart failure. In this review, it was found that the use of RAAS inhibitors and beta-blocker drugs reduced the incidence of cardiotoxicity.

Study Characteristics

The study design and population characteristics of included studies are presented in Table 1. Mean patient ages ranged from 40-57 years old, and some studies included cardiac disease and the use of heart drugs. Furthermore, all the study participants were only breast cancer patients.

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Figure 1. PRISMA flow diagram
A total of 19 eligible studies were found, consisting of 2 cohort studies, 16 trials, and 1 retrospective case-control. The breast cancer treatments were ANT and Trastuzumab. Eleven reports assessed the effect of the cardio-protective drug on ANT and nine assessed the impact of Trastuzumab. The type of ANT used in all the studies was Doxorubicin and Epirubicin.

LVEF with echocardiography, cardiac MRI, MUGA, and echocardiography and MUGA were analyzed in 15 [9-13,15-22,25,26], 2 [14,23], 1 [27], and 1 [24] studies, respectively. Cardiac biomarkers, such as NT-pro-BNP, cardiac troponin, and cardiac troponin T were examined in 3 [12,16,22], 3 studies [11,14,16], and 2 [18,22] studies, respectively. A total of 3 articles described the interruption of Trastuzumab therapy because of cardiotoxicity and LV dysfunction [23,24,27].

The mean follow-up time for echocardiography outcome ranged between 14 days and 3.5 years after the beginning of chemotherapy, with most reports’ follow-up time being 6 months. A total of four studies had follow-ups of 3 months [10,18,19,20], while 2 studies had a time range of 3.5 years [25,26].

Based on the results, eight, one, one, three, two, one, one, one, and one studies used Beta-blocker as cardio-protective strategies [9-13,19-21], ARB [22], a combination of ARB and Beta-blocker [14], a combination of ACE-inhibitor (ACE-I) and Beta-blocker [15,23,24], a combination of ACE-I/ARB/BB [25,26], spironolactone [16], statin [27], Dexrazoxane [17], and exercise [18], respectively.

Comparators were placebo or control groups with no intervention. Among eight studies using Beta-blockers alone, six studies used Carvedilol [9-11,19-21], with doses ranging from 6.25 mg titrated to 25 mg twice a day, with one study utilizing a combination of Carvedilol 10 mg and Lisinopril 10 mg [24]. Furthermore, metoprolol was used in one study, compared with the use of Candesartan [14]. In one article, Bisoprolol was started 24 hours before chemotherapy, with a starting dose of 1.25 mg and the combination of Lisinopril 2.5 mg, both were titrated until they reached a target dosage of 10 mg [15]. Another report used Bisoprolol 2.5 mg and Perindopril 2 mg, initiated 7 days before the start of chemotherapy and was titrated as tolerated, with target doses of 10 mg and 8 mg, respectively [23]. A total of two studies utilized Nebivolol 5 mg as the main treatment agent [12,13]. Dexrazoxane was administered in one report and started 30 minutes before ANT [17]. Spironolactone 25 mg was reported in only one study and was given 1 week before the therapy [16]. Vigorous intensity exercise of 30 minutes that was performed 24 hours before each chemotherapy until the 4th cycle, was used as a cardioprotective strategy in one article [18]. Statins in moderate to high intensity (Atorvastatin 20 mg, Rosuvastatin 10 mg, Simvastatin 20 mg, and Pravastatin 20 mg) were used in another article [27].

Candesartan 16 mg was used in one study, started on the first day of chemotherapy administration, and titrated until a final dose of 32 mg [22]. A total of two studies did not specify the drug names of RAAS inhibitors and B-blockers [25,26].

**Primary Outcomes**

The outcomes assessed by this systematic review were the change in mean LVEF by 10% or more from the baseline value. LVEF was examined two times, by comparison of the value before chemotherapy in the control group and intervention group with the value obtained after follow-up in each study. LVEF was evaluated by echocardiography, cardiac MRI, or MUGA.

The results showed that carvedilol was not significant in preventing the reduction of LVEF >= 10% from baseline (p-value > 0.05 in seven studies) during ANT or Trastuzumab therapy [9–11,19–22]. This effect was observed in 3 months, 6 months, and 12 months from the first day of chemotherapy. According to Farahani et al. [19], Carvedilol 6.25 mg twice a day during Trastuzumab therapy increased the LVEF by 0.28% from baseline, but the p-value was not significant.

Cochera et al. [13] reported the use of Nebivolol 5 mg on 60 participants throughout the duration of the 6th cycle of Doxorubicin therapy. The results showed that the treatment was not significant in causing changes to LVEF. However, Kaya et al. [12] reported a significant impact of Nebivolol 5 mg (p = 0.01) in preventing the decrease of LVEF during Epirubicin therapy in 6 months follow-up. The treatment was given 7 days before the start of chemotherapy until the end of the process.

Boekhout et al. [22] studied the effect of Candesartan 16 mg in 210 patients who underwent Trastuzumab therapy with/without ANT therapy. This study found no difference in the reduction of LVEF between the treatment group and the placebo group. However, the value in the Candesartan group was found to be reduced by 3%, compared to the reduction of 1.2% in the placebo group.

A study by Gulati et al. [14], which was a PRADA trial, reported the use of Metoprolol and Candesartan versus placebo in 130 patients receiving ANT with or without Trastuzumab during 18 months of the follow-up period. Candesartan was started on 8 mg and titrated as tolerated until the target dose of 32 mg, as well as Metoprolol, which was started on 50 mg and finally reached 100 mg. In the Candesartan group, there was a significant decrease in LVEF reduction (-0.8%, p-value = 0.026) compared to the Metoprolol and Placebo group.

Wihandono et al. [15] evaluated the combination of Lisinopril and Bisoprolol in 51 patients who underwent the 6th cycle of ANT therapy. The treatment was started 24 hours before the 1st cycle of chemotherapy. Lisinopril and Bisoprolol were started from the smallest dose, which was 2.5 mg and 1.25 mg, respectively until it reached the maximal dose of 10 mg. The decline of
LVEF was significantly reduced in the combination group compared to the placebo group (p-value 0.017). The effect of Lisinopril was also observed in the study by Guglin et al. [24], alongside the impact of Carvedilol and placebo at 2 year-follow up. The results showed that there was no significant difference in LVEF reduction > 10% from baseline value in all of the groups. However, the interruption caused by cardiotoxicity (decrease in LVEF) was lower in patients who received Lisinopril and Carvedilol, namely 30%, 29%, and 32% of the lisinopril, carvedilol, and placebo groups. Pituskin et al. [23], in the MANTICORE trial, reported the impact of a combination of Perindopril and Bisoprolol that was initiated within 7 days before the start of chemotherapy. Bisoprolol and Perindopril attenuated the decline in LVEF by -1% and -3%, respectively, with a p-value of 0.001.

In a study by Khoury et al. [25], the SAFE-HEaRt trial, in the long-term follow-up of 3.5 years reported improvement of LVEF (+7.2%) compared to baseline. The study used B-blockers and/or ACE-I/ARB but did not specify the name of the drugs. Ohtani et al. [26] also reported that heart failure treatments (Renin-Angiotensin Inhibitors and/or B-blockers) decreased its reduction and enhanced the functional reversibility of LV systolic dysfunction.

The cardio-protective effect of Spironolactone 25 mg was reported in one study by Akpek et al. [16]. The treatment was started one week before chemotherapy and was followed up for six months. Furthermore, spironolactone significantly reduced the decrease in LVEF compared to the control group with a p-value < 0.001. A study by Kim et al. [17] evaluated the impact of Dextrazoxane (DZR) which was administrated 30 minutes before Doxorubicin. LVEF was higher in the DZR group, hence, DZR reduced cardiac toxicity and delayed the timing of cardiac toxicity (p < 0.001). Moderate to high intensity of statin was observed in the study by Calvillo et al. [27] with a follow-up duration of 11 months. Statin lowered the reduction of LVEF (p 0.016) and the risk of cardiotoxicity (OR 0.32, 95% CI 0.10–0.99, p = 0.049). Kirkham et al. [18] in a study utilizing exercise as a cardio-protection strategy for treatment. Vigorous exercise was started 24 hours before each chemo and the intervention was carried out in thirty minutes. After the 4th cycle of chemotherapy, the LVEF was evaluated and there was no effect of exercise in attenuating the reduction of LVEF. However, the study did not exclude the use of cardiac medications.

**DISCUSSION**

This study reported the cardioprotective interventions that had been tested by several randomized controlled trials and cohort studies, including treatment with RAAS inhibitors, beta-adrenoceptor blockers, statin, Dextrazoxane, and exercise. Based on the results, the cardioprotective effect of RAAS inhibitors (ACE-I, ARB) and Beta-blockers were proven effective for the treatment and prevention of heart failure. This indicated that these drugs were beneficial in attenuating the cardiotoxic impact of chemotherapy. However, the outcomes of these medications and strategies as cardioprotection on patients who underwent chemotherapy varied. Included trials and studies reported modest or no effect of the interventions on the primary outcome of this review.

Several guidelines recommended the routine measurement of ANT and trastuzumab-induced cardiotoxicity through echocardiography, particularly the LVEF [28,29]. According to previous studies, chemotherapy reduced LVEF and induced the incidence of heart failure. When heart failure was detected during a routine echocardiography measurement, current oncologic guidelines recommended suspending chemotherapy for patients experiencing heart failure with a left ventricular ejection fraction (LVEF) below 50%, a decline in LVEF to less than 40%, or a substantial drop in EF (15% absolute percentage points) to less than 50%. In such cases, treatment with an ACE inhibitor (ACE-I) or an angiotensin receptor blocker (ARB), along with a beta-blocker must be initiated. Clinicians must also treat patients with heart failure using standard care [30,31].

Apart from LVEF, other parameters that must be carefully monitored include cardiac biomarkers. ESC and AHA recommended NT pro-BNP as class 1A recommendations in diagnosing patients with suspected heart failure (HF). Changes in Troponin concentrations could be used to predict cardiomyocyte injury. Therefore, the measurement of cardiac biomarkers could evaluate and predict the subsequent changes in LVEF and the development of HF.

The end-points of this study were to evaluate the positive effect of strategies that could prevent or reduce the cardiotoxicity event during chemotherapy. Despite the various results of the included studies, the reduction of LVEF occurred only in a smaller proportion of patients who received cardioprotective strategies. A similar perspective was also seen in the interruptions of chemotherapy due to heart failure occurrence. In most studies, there was no interruption, while it occurred at low levels in some studies in the cardioprotection group.

This study had several limitations, including the use of different ACE-I, ARB, Beta-blockers, statin, and other strategies. Furthermore, there were different endpoints, timing of intervention starting points, durations of follow-up periods, and chemotherapy dose, making it difficult to conclude the effects of these cardioprotective interventions. The sample size was also very small and could not represent the real populations. Some of the included studies did not exclude the participants with a history of heart disease (coronary artery disease (CAD),
Hypertension, HF, valvular heart disease, arrhythmia), and cardioactive medications (ACE-I, statin, CCB, ARB, B-blockers, anti-aldosterone, and other adrenergic beta-blockers). Further studies are advised to include larger populations with homogeneity of pre-existing conditions and the same timing of cardioprotective therapy administration, as well as a longer follow-up period. The early diagnosis of heart failure could also be measured by the value of strain and strain rate parameters, apart from LVEF. In previous studies, LVEF was found to be reduced after a late period of toxic damage to the myocardium. Therefore, another assessment, such as GLS or other strain endpoints could be a sensitive method to detect the early signs of myocardial damage. Cardiac biomarker sampling must also be monitored closely during chemotherapy cycles as the early checkpoint of cardiotoxic effects.

CONCLUSIONS

This systematic review suggested the cardioprotective effect of RAAS inhibitors or Beta-blockers in reducing CTRCD (Cancer-Therapy Related Cardiac Dysfunction). Other strategies, such as statins, Spironolactone, exercise, or DZR must be evaluated in more studies, as the data included in this systematic review were limited. Studies on the accurate effect of cardioprotective strategies must be continued to develop more targeted approaches.

DECLARATIONS

Competing interest
The authors declare no competing interest in this study

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Not applicable

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REFERENCES


