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Rationale and Design of the Prevention of Cardiac Dysfunction during an Adjuvant Breast Cancer Therapy (PRADA) Trial

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Key Words
Breast cancer · Cardiotoxicity · Cardiovascular magnetic resonance · Echocardiography

Abstract
Objective: The PRevention of cArdiac Dysfunction during Adjuvant breast cancer therapy (PRADA) study is a randomized, placebo-controlled, double-blind trial to determine whether angiotensin receptor blockers (ARB), or beta-blockers or their combination may prevent the development of left ventricular (LV) dysfunction in patients on standard adjuvant treatment for early breast cancer. ***Methods:*** Following surgical resection, 120 breast cancer patients scheduled for adjuvant epirubicin-containing chemotherapy and, if indicated, trastuzumab, will be included. They will be randomized to an ARB (candesartan), a beta-blocker (metoprolol) and matching placebos in a 2 × 2 factorial design. The primary objective of the PRADA study is to assess whether prophylactic ARB and/or beta-blockers may prevent a reduction in LV ejection fraction (EF) after adjuvant treatment of early breast cancer, as evaluated by serial cardiovascular magnetic resonance (CMR) performed at randomization, after the first chemotherapy cycle and on its completion, and for subgroups, on completion of radiotherapy or trastuzumab. Secondary outcome measures include echocardiographic indices of LV diastolic dysfunction, structural myocardial alterations assessed by CMR and changes in cardiac biomarkers. ***Conclusion:*** PRADA may provide new information on the prophylactic effect of ARB and beta-blockers in patients with early breast cancer regarding the risk of developing cardiac dysfunction from adjuvant cancer treatment.

Background and Scientific Rationale

Breast cancer is currently the most common malignancy among women worldwide [1]. Recent improvements in its detection and treatment have resulted in

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survival gains [2]. Adjuvant therapy in early breast cancer typically includes anthracycline-containing chemotherapy, sometimes followed by taxanes, the anti-ERBB2 (-Her-2) agent trastuzumab and radiotherapy, each modality contributing to an increased risk of cardiac disease including atherosclerotic coronary artery disease and left ventricular (LV) systolic and diastolic dysfunction. In a subgroup of patients, the cardiovascular impairment may progress to clinically overt heart failure [3, 4].

Anthracyclines are believed to cause immediate damage to cardiac myocytes by (1) activating calcium channels resulting in intracellular calcium overload and reduced cardiac contractility, and (2) by generating reactive oxygen species that induce sarcomere degeneration, mitochondrial dysfunction, DNA damage and alteration of gene expression that cause apoptotic and necrotic cell death [5, 6]. The incidence of cardiotoxicity increases with cumulative dose; however, even low doses of epirubicin in adjuvant chemotherapy for breast cancer have been shown to result in a mild impairment of LVEF, a rise in B-type natriuretic peptide (BNP) levels, and increased QT interval (QTc), all of which may indicate an increased risk of subsequent heart failure (HF) development [7]. Reported HF rates associated with epirubicin range from 0.6% at a cumulative dose of 550 mg/m^2 to 14.5% at a cumulative dose of 1,000 mg/m^2 [8]. Cardiac dysfunction may occur immediately or more commonly, months or years after finishing chemotherapy [8]. Typical histopathological findings in the myocardium include vacuolization of myofibrils, decreased size of muscle fibers, interstitial edema and fibrosis [9].

Trastuzumab, a monoclonal antibody that binds to the extracellular portion of the transmembrane receptor ERBB2 (Her-2) on the cardiac myocyte is also associated with cardiac dysfunction. One to three percent of patients treated with trastuzumab will develop clinically apparent LV dysfunction, while 5–17% will experience an asymptomatically decreased LVEF. The mechanisms for the LV systolic and diastolic dysfunction by trastuzumab are not fully established, but seem related to reduced protection from stress pathways [10]. The pivotal role of ERBB2 in the myocardium was reported already a decade ago in ERBB2 knock-out mice developing dilated cardiomyopathy [11]. More recent experimental data demonstrate that trastuzumab mediates a deleterious effect on cardiomyocytes mainly by inducing the production of reactive oxygen species [12], which eventually will lead to mitochondrial membrane depolarization, ATP depletion and contractile dysfunction [13]. Although trastuzumab-induced cardiomyopathy has been reported to be partly reversible, the combined therapy of trastuzumab and anthracyclines has been found to impair LV function in almost a third of patients [13].

The additional strain on the cardiovascular system by radiotherapy is well-established [14], including a potential hazard for the development of both ventricular dysfunction and coronary artery disease. Radiation-induced toxicity is typically late-occurring and comprises diffuse fibrotic and microvascular damage of the myocardium, while the atherosclerotic burden of the coronary arteries often induces premature coronary artery events [15]. Although highly conformal radiotherapy techniques reduce the heart volume at risk, especially in patients treated for left-sided breast cancer [4], radiation-induced detrimental late effects are long-term side effects in this particular patient group and add to the adverse effects of the other therapeutic modalities.

Heart failure is associated with complex neuroendocrine activation, and neuroendocrine blockade with angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs) and beta-blockers have proven efficient in reducing mortality and morbidity in all stages of HF. Moreover, ACEIs have been shown to prevent or delay the development of symptomatic HF in patients with asymptomatic LV dysfunction [16, 17]. There are indications that asymptomatic cardiotoxicity may leave the heart vulnerable for added stressors, which could progress to late-onset cardiac events [18] and, therefore, early intervention with established HF regimens may prove beneficial. Previous studies indicate that prophylactic use of established HF therapies in the setting of anthracycline-induced cardiotoxicity may prevent or reduce adverse effects. However, the majority of these studies have been done in heterogeneous patient groups with different types of cancer and treatment regimens [19–23]. Currently, there are no results available in the literature from randomized trials concerning the prophylactic effect of beta blockers, ACEIs or ARBs in patients receiving standard adjuvant oncologic therapy for early breast cancer.

Cardiovascular magnetic resonance imaging (CMR) has become a reference standard for the measurement of cardiac volumes, function and mass, as it offers high accuracy, reliability and reproducibility [24]. CMR also permits visualization of morphologic changes in the myocardium, and is therefore widely used to assess myocardial injury. In CMR, myocardial inflammation is associated with both edema (reflected in increased sig-

nals in T2-weighted images) and hyperemia (assessed by an increment in early enhancement). Irreversible myocardial damage and fibrosis can be visualized with late-enhancement techniques [25]. Pertinent to the PRADA study, Wassmuth et al. [26] examined 22 anthracycline-receiving patients by contrast-enhanced MRI technique and found that patients exhibiting increased myocardial contrast enhancement on day 3 after anthracycline injection were at an increased risk of a later decrease in LVEF. Moreover, in a rat model, Lightfoot et al. [27] demonstrated an association between increased gadolinium signal intensity on T1-weighed CMR, subsequent LVEF reduction and histopathological evidence of anthracycline-induced cardiotoxicity.

Important advances have been made in cardiac ultrasound technology during the two past decades. With the introduction of 'second harmonic imaging' in the 1990s, 2-dimensional images were clearly improved without impairment of other standard echocardiographic techniques, such as pulsed or continuous Doppler [28]. During the last 10 years, tissue velocity imaging (TVI) where velocity measurements can be applied directly on the myocardium (locally or on the entire myocardium) has been developed, and with TVI strain, a derivative method, systolic myocardial deformation can be assessed [29]. Two-dimensional strain echocardiography makes it possible not only to measure longitudinal, but also radial and circumferential systolic deformation of the right and left ventricle [30]. These new methods have been demonstrated to be more sensitive in detecting changes in diastolic and systolic LV function than standard echocardiography. The application of these new techniques for the assessment of right ventricular (RV) and LV function is in an early phase. Real-time 3-dimensional echocardiography is another recent development in cardiac ultrasound, not yet in clinical use due to the previous time-consuming procedure [31]. However, newer real-time software makes it possible to examine patients and calculate ventricular volumes in much less time [31].

Although CMR is the reference standard for the assessment of cardiac volumes and thus both RVEF and LVEF, echocardiography, through measurement of transmitral flow and, in part, TVI, is currently considered the preferred tool for the evaluation of LV diastolic function.

Based on this background information, we designed a randomized trial to evaluate the potential of ARBs or beta-blockers or both, started before chemotherapy to prevent a decline in systolic LV function as assessed by CMR and diastolic LV function as assessed by echocardiography.

The PRADA Study

Design and Objectives

The PRADA study is a randomized, placebo-controlled, 2 × 2 factorial, double-blinded trial. The primary objective of the study is to assess whether the ARB candesartan, the beta-blocker metoprolol or a combination of the two can prevent a reduction in LVEF as measured by CMR in patients receiving adjuvant oncologic therapy for early breast cancer.

Secondary objectives are:

- to longitudinally evaluate morphological changes of the myocardium using CMR in patients receiving adjuvant oncologic therapy for early breast cancer
- to evaluate correlations between cardiac morphological changes after adjuvant oncologic therapy for early breast cancer, and subsequent changes in cardiac function
- to assess the prophylactic effects of candesartan, metoprolol or a combination of both on change in LV diastolic function as assessed by echocardiography, during adjuvant oncologic therapy for early breast cancer
- to assess the potential of cardiac biomarkers to identify patients at risk of cardiac impairment after adjuvant oncologic therapy for early breast cancer, and to assess interactions between treatment response and biomarker dynamics
- to compare the assessment of LV systolic function between CMR and echocardiography by its novel applications as TVI, 2-dimensional strain and 3-dimensional echocardiography.

Participants

Following written, informed consent, patients aged 18–70 years who have undergone breast cancer surgery and who are scheduled to receive adjuvant chemotherapy at the Department of Oncology, Akershus University Hospital, Norway, are eligible for inclusion in the PRADA study. Inclusion and exclusion criteria are listed in table 1.

Randomization Procedure

In accordance with the recommendations of the Norwegian Breast Cancer Group, patients will receive one of the adjuvant chemotherapy regimens listed in table 2.

A block randomization procedure stratified for trastuzumab therapy will be used. We expect minimal cardiotoxic effects of taxanes, endocrine therapy and conformal radiotherapy, and no stratification for these parameters will be performed.

Intervention

Candesartan, metoprolol and a matching placebo will be provided in a 2 × 2 factorial manner. Dose titration will begin after randomization but before the initiation of chemotherapy. Candesartan/placebo will be initiated at 8 mg o.d. and titrated up to a target dose of 32 mg o.d. Metoprolol/placebo will be initiated at 25 mg o.d. and titrated up to a target dose of 100 mg o.d. The duration of the blinded intervention period will be the period of adjuvant therapy. If the patient develops symptoms of hypotension after dose titration is completed, metoprolol/placebo will be reduced by 25 mg at a time before the reduction in the candesartan/placebo dose of 8 mg is initiated. If the patient develops symptoms of bradycardia after dose titration is completed, metoprolol/placebo will be reduced by 25 mg at a time. Patients unable to reach or maintain the target dose will continue in the study on the achieved doses, in accordance with the intention-to-treat principle. In case of a cardiac event requiring therapy, open-label therapy with an ACE inhibitor, ARB or beta-blocker may be considered.

Blinding

All investigators will be blinded to drug allocation, group and the order of MRI and echocardiography.

Evaluations

On inclusion, patient demographics and medical history will be recorded. A physical examination will be performed, including the measurement of blood pressure and pulse rate. In addition, an electrocardiogram (ECG) will be recorded. Venous blood samples will be obtained in order to measure creatinine, hematocrit, electrolytes and biomarkers. CMR and blood samples will be obtained (1) on randomization, (2) on completion of the first chemotherapy cycle and (3) on completion of chemotherapy, and in the subgroup receiving additional therapy (4) on completion of radiotherapy or trastuzumab. Echocardiography will be performed (1) on randomization, (2) on completion of chemotherapy, and in the subgroup receiving additional therapy (3) on completion of radiotherapy or trastuzumab (fig. 1)

CMR Protocol

All participants will be examined with a 1.5-T MRI scanner (Achieva; Philips Medical Systems, Best, The Netherlands), using advanced cardiac software, vector-ECG triggering and a 5 element phased-array cardiac coil, except for the T2 STIR images where a body coil will be used.

Table 1. Inclusion and exclusion criteria in the PRADA study

Inclusion criteria
Women aged 18–70 years
Eastern Cooperative Oncology Group performance status 0–1
Serum creatinine ≤140 μmol/l or estimated creatinine clearance ≥60 ml/min (using the Modification of Diet and Renal Disease formula)
Systolic blood pressure ≥110 and ≤170 mm Hg
LVEF ≥50%
Exclusion criteria
Hypotension, defined as systolic blood pressure <110 mm Hg
Bradycardia, defined as heart rate <50 b.p.m.
Prior anthracycline chemotherapy regimen
Prior malignancy requiring chemotherapy or radiotherapy
Symptomatic heart failure
Systolic dysfunction (LVEF <50%)
Clinically significant coronary artery disease, valvular heart disease, significant arrhythmias or conduction delays
Uncontrolled arterial hypertension defined as systolic blood pressure >170 mm Hg
Treatment with ACEI, ARB or beta-blocker within the last 4 weeks prior to study start
Intolerance to ACEI, ARB or beta-blocker
Uncontrolled concomitant serious illness
Pregnancy or breastfeeding
Active abuse of drugs or alcohol
Suspected poor compliance
Inability to tolerate the MRI scanning protocol, e.g. claustrophobia, weight >120 kg, etc.

Table 2. Estimated distribution of adjuvant chemotherapy regimens

Regimen		Approximate percentage of all patients
FEC 60 × 6		30
FEC 60 × 4	followed by taxanes for 12 weeks	50
FEC 100 × 4	followed by trastuzumab[1] given simultaneously with taxanes in the beginning (only during the first 12 weeks); in total 17 cycles of trastuzumab every 3 weeks	20

FEC 60 = 5-Fluorouracil 600 mg/m^2, epirubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 every 3 weeks; taxanes = paclitaxel 80 mg/m^2 once weekly for 12 weeks or docetaxel 100 mg/m^2 every 3 weeks for 12 weeks; trastuzumab 8 mg/kg i.v. (loading dose) followed by 6 mg/kg i.v. every 3 weeks, in total 17 cycles. FEC 100 = 5-Fluorouracil 600 mg/m^2, epirubicin 100 mg/m^2 and cyclophosphamide 600 mg/m2 every 3 weeks.

[1] Initiated 3 weeks after the last cycle of anthracyclines.

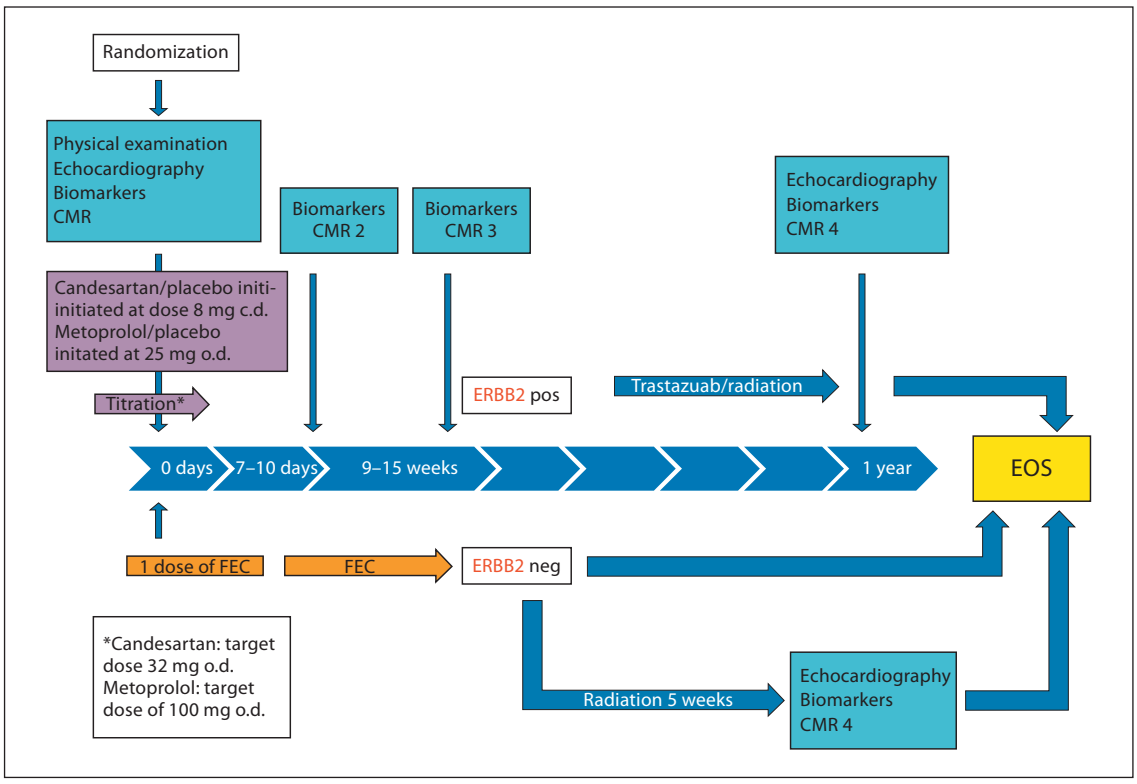

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Fig. 1. Flow chart of study procedure. EOS = End of study; FEC = 5-fluorouracil, epirubicin and cyclophosphamide; neg = negative; pos = positive.

Myocardial function and dimensions, including LV wall thickness, end-systolic and end-diastolic volume, permitting the assessment of LV mass, EF and LV remodeling index, will be assessed by CMR, using breath-hold Steady-State-Free-Precession sequences (SSFP) in contiguous short-axis images covering the entire LV. LVEF decrement is defined as an absolute decrease in LVEF >10%, associated with a decline below its normal limit of 50%. We will assess cardiac edema with conventional short axis breath-hold, black-blood triple inversion recovery T2 imaging and fibrosis with phase-sensitive inversion recovery late-enhancement imaging 15 min after intravenous injection of 0.2 mmol/kg Gadolinium-DOTA (Dotarem, Guerbet, France). In a subgroup, we will also apply T1 mapping by the Modified Look-Locker inversion recovery (MOLLI) sequences. The scanning parameters will be as previously described [25, 32].

MRI Analysis

Image analysis will be performed with dedicated software by a board-certified radiologist. LVEF will be calculated by tracing the LV endocardial contours in end-diastole and end-systole of the short axis images. The T2 ratio between myocardium and skeletal muscle will be calculated as described by Friedrich et al. [25]. T1 maps will be calculated with dedicated software, and late gadolinium enhancement images will be evaluated for regions of focal enhancement as a sign of fibrosis.

Echocardiography

Transthoracic echocardiography will be performed by using a Vivid E9 (GE Healthcare, Horten, Norway). Images will be digitally stored for offline analysis on custom software (Echopac, GE Vingmed, Horten, Norway). Two-dimensional images and loops will be acquired with a 2.5-MHz transducer and 3-dimensional images with a 4-volt matrix-array transducer. Standard parasternal long axis and three apical view recordings will be done in the end-expiratory phase with the subjects in the supine left lateral position. LV dimension, septal and posterior wall thickness and LV mass will be measured as recommended by American Society of Echocardiography. LVEF will be calculated using the modified Simpson's rule from biplane 4-chamber and long-axis views. LV diastolic

function will be assessed by pulsed Doppler transmitral peak early (E), peak late (A) and E deceleration time. TVI-derived indices will be recorded at the base of the septal and lateral mitral annulus to determine peak systolic (S'), early diastolic (e') and late (a') diastolic velocities. Global longitudinal systolic strain will be analyzed by an offline semi-automated speckle tracking technique from the three apical views. Specific 3-dimensional recordings will be performed from the apical view by storing four heart cycles and offline analyses of LV volumes (TomTec Imaging Systems, Germany).

Blood Sampling Procedures and Biochemical Assays

Venous blood samples are to be obtained for measuring circulating concentrations of established and novel cardiac biomarkers. In addition to measurements of the established cardiac biomarkers (1) high-sensitivity cardiac troponin T (hs-cTnT) and high-sensitivity cardiac troponin I (hs-cTnI), (2) BNP and N-terminal pro-BNP (NT-proBNP), we plan to measure (3) inflammatory and anti-inflammatory mediators like hsCRP, TNF-alpha, sCD40 ligand, IL-6, IL-10, and various chemokines, (4) markers of cardiac fibrosis like collagen markers and (5) markers of oxidative stress like isoprostanes. Other novel markers like circulating nucleic acids will also be considered. Cardiac troponin concentrations will be assessed in relation to the 99th percentile value of a healthy population, i.e. 14 ng/l (hs-cTnT, Roche Diagnostics, Penzberg, Germany) and 16 ng/l (hs-cTnI: ARCHITECT STAT High-Sensitivity Troponin, Abbott Diagnostics, Abbott Park, Ill., USA) and the proportion of subjects with detectable troponin levels. BNP and NT-proBNP will be measured with established assays and we will use the cut-offs of 100 ng/l and 300 ng/l, respectively, according to current guidelines. However, measurements of cardiac troponins, BNP and NT-proBNP will mainly be entered in the statistical analyses as continuous variables, as levels below the cut-offs are also indicative of cardiac injury and myocardial dysfunction in stable patients. All blood samples will be sampled by dedicated study personnel with serum vacutainers kept at room temperature and EDTA vacutainers collected on ice, followed by centrifugation at 4°C. After processing, samples will be stored in 500-μl vials at –80° pending analysis.

Statistical Considerations

Data analysis

All analyses will be performed according to the intention-to-treat principle. Between-group comparisons will be performed by means of the χ^2 test or the Fisher exact test for categorical data and the paired t test or the Mann-Whitney U test for continuous variables, as appropriate. Logistic regression and linear regression analysis will be performed to assess the effect of the interventions. Potential interaction between the two interventions and outcome will be assessed by applying the likelihood ratio test to models with an interaction term and those without the interaction terms. The contribution of left- versus right-sided radiation and the effect of chemotherapy regimens and trastuzumab to LV dysfunction will be assessed by logistic and linear regression analyses. Predictors of long-term cardiovascular events will be assessed by means of the Cox regression analysis. All tests will be two-tailed, and results will be considered significant at $p < 0.05$.

Power Calculations

The power calculations are based on the following assumptions: baseline LVEF is 60% [±5% (SD)] and alpha is 0.025. With 100 patients included (i.e. 25 patients per arm) the trial will have >90% power to detect an absolute difference in LVEF of 5% between the placebo and the beta-blocker and ARB groups, respectively. A 5% difference is deemed to be clinically relevant.

There will be no interim analysis and, accordingly, there will be no modification of p value thresholds or statistical stopping rule for the trial. A maximum of 20% dropout is anticipated, and the targeted inclusion will therefore be 120 patients.

Study Approval and Progression

The study protocol has been approved by the regional ethics committee, and the protocol is registered in the clinicaltrials.gov registry. A data and safety monitoring board has been constituted to ensure the safe continuation of the study.

Current Status

Patient inclusion in the interventional part of the study started in September 2011 and is expected to be completed by September 2013. At the end of August 2012, 51 patients have been enrolled.

Discussion/Clinical Implications

The cardiotoxic effects of modern adjuvant cancer therapy may cause significant morbidity in an increasing number of breast cancer survivors. Both ACEI and beta-blockers have shown promising results in preventing or

reducing anthracycline-induced LV dysfunction. However, the majority of these studies have been done in heterogeneous patient groups with different types of cancer and different treatment regimens. After demonstrating that increased troponin I levels after high-dose chemotherapy is a strong predictor of subsequent LV dysfunction, Cardinale et al. [33, 34] conducted an open, randomized trial of ACEI therapy in 114 troponin I-positive patients with diverse malignancies who received different types of high-dose anthracycline-containing regimens. The main result of this study was a favorable outcome regarding cardiovascular events and LVEF deterioration in patients on ACEI therapy <1 month after the completion of chemotherapy and who then continued ACEI therapy for 12 months [19]. However, this was an open-labeled study without placebo controls, and while treatment started early (1 month after completion of high-dose chemotherapy), it did not explore the effect of preventive HF treatment. The study population also included several different oncological diseases and chemotherapeutic regimens, thus not permitting conclusions to be made regarding specific groups of cancer patients. Moreover, data from an open, nonrandomized trial of 201 patients with anthracycline-induced cardiomyopathy indicates that, if initiated early, the combination of a beta-blocker and an ACEI may result in LV functional recovery [20], and that a short time until HF treatment is an independent predictor of LVEF recovery. Analogous to other previous studies, this study also included different malignancies and anthracycline regimens, and treatment was initiated only after signs of cardiotoxicity had been identified. Furthermore, there was no placebo control group, and all patients received both beta-blocker and ACEI, which precludes drawing conclusions regarding the individual effects of beta-blockers or ACEIs in preventing chemotherapy-induced cardiovascular dysfunction. Recently, some smaller randomized studies have emerged. In 1 of these, 40 lymphoma patients were randomized to either prophylactic ACEI or no ACEI therapy for 7 days concurrently with standard chemotherapy [22]; this study showed that the local renin-angiotensin system may play a critical role in acute chemotherapy-induced cardiotoxicity, which seemed to be attenuated by prophylactic treatment with ACEI. The limitations of the study were a small number of patients, a lack of placebo controls, the short treatment and the short follow-up of 7 days. A more recent, placebo-controlled study of 49 patients receiving anthracyclines found that ACEI may reverse early myocardial impairment [23]; this study was also limited by its small number of patients, short follow-up of 7 days and the inclusion of different malignancies.

In contrast to ACEI, there is limited information on the potential prophylactic effects of beta-blockers in patients receiving adjuvant chemotherapy. Using echocardiographic techniques, Kalay et al. [21], in a randomized, placebo-controlled study of 50 patients with different malignancies, showed that carvedilol may protect against chemotherapy-induced LV systolic and diastolic dysfunction. Study limitations were the low number of patients and the inclusion of different malignancies.

In each of these studies, LV function was evaluated by echocardiography. There are no published results of proven HF therapy to prevent cardiotoxicity in patients with early breast cancer receiving trastuzumab, but an ongoing placebo-controlled study of the prophylactic effect of ACEI and beta-blocker assessed by CMR is currently including patients [35].

All of the previous studies have provided valuable insights into the potential of HF therapy to protect from cardiovascular damage caused by adjuvant chemotherapy, but larger studies with an optimal design are needed to advance the field further. The strengths of the PRADA study are the prospective, randomized, placebo-controlled, double-blinded design, the homogenous group of participants and the study of the complete course of adjuvant therapy for early breast cancer. The high accuracy and reproducibility of CMR for the quantification of cardiac volumes and LVEF, and the added sensitivity of echocardiography for signs of diastolic dysfunction will enable detection of subtle changes in heart function. The assessment of cardiac biomarkers will also provide additional metrics to identify patients at risk of cardiac injury and for the stratification of patients concerning the effects of treatment. By including CMR evaluation during the course of adjuvant therapy, we will also be able to provide information on early and late structural and morphological changes to the myocardium after cancer therapy as well as the relationship of these changes to alterations in biochemical and echocardiographic parameters. This work will contribute to the effort of preventing, detecting and treating the cardiotoxic effects of cancer therapy.

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