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RESEARCH LETTERS

Effect of Eplerenone on Diastolic Function in Women Receiving Anthracycline-Based Chemotherapy for Breast Cancer

Anthracycline agents are commonly used in early breast cancer but are associated with dose-related cardiotoxicity. Diastolic dysfunction may be more common and occur earlier than systolic dysfunction (1,2). Eplerenone is an oral mineralocorticoid antagonist (MRA); these agents prevent myocardial structural changes that result in systolic and diastolic dysfunction in many disease states and reduce cardiovascular mortality and heart failure-related hospitalization among patients with heart failure (3).

ELEVATE (Effect of Eplerenone on Left Ventricular Diastolic Function in Women Receiving Anthracyclines for Breast Cancer) was a single-center prospective randomized placebo-controlled trial. It was designed to test the hypothesis that administration of eplerenone for 6 months during treatment of breast cancer with anthracycline-based chemotherapy would have positive effects on diastolic performance, as measured by average early diastolic tissue velocity of the mitral annulus (E'_{avg}), in women receiving anthracycline-based chemotherapy for early or locally advanced breast cancer.

The study protocol was approved by the UBC Clinical Research Ethics Board (University of British Columbia, Vancouver, British Columbia, Canada). All subjects provided informed consent before randomization. ELEVATE was registered at ClinicalTrials.gov (NCT01708798). An independent Data Safety Monitoring Board monitored the safety and efficacy of the trial and assessed periodically whether the trial should continue.

The study patients included anthracycline-naïve women ≥19 years of age with normal left ventricular (LV) systolic function, serum potassium ≤5.0 mmol/l, and stage I to III breast cancer, who were scheduled to undergo curative treatment with a doxorubicin-based chemotherapy regimen. Patients were randomized in a 1:1 ratio to eplerenone, with a target dose of 50 mg daily, or placebo, stratified by concomitant trastuzumab therapy. Patients, treating physicians, and study personnel responsible for collecting data were blinded to treatment assignments.

Study drug administration began a minimum of 2 days before starting anthracycline therapy. Potassium levels were checked at 1 week, at 4 weeks, and 1 week following any dose increase.

Subjects were treated with an adjuvant or neoadjuvant doxorubicin-containing chemotherapy regimen as recommended by their treating oncologist. All patients received 4 cycles of doxorubicin 60 mg/m^2 intravenously every 2 or 3 weeks for a total cumulative dose of 240 mg/m^2. Patients with HER2 (human epidermal growth factor receptor-2) overexpressing breast cancer also received trastuzumab.

Transthoracic echocardiograms were performed by an advanced sonographer and interpreted by a level 3 certified echocardiographer. All measurements were performed in a standard fashion in accordance with American Society of Echocardiography (ASE) criteria (4).

The primary outcome of ELEVATE was change in E'_{avg} after 6 months, as measured by transthoracic echocardiograms. E'_{avg} was selected as a relatively preload-independent measure with greater power to discriminate between normal and abnormal diastolic function than standard Doppler flow indices (4). Secondary outcomes included the following: changes in additional measures of diastolic function; changes in systolic function; proportions of patients with diastolic function worsening by ≥1 ASE grade (4); proportions of patients with a decline in systolic function, defined as a decline in LV ejection fraction (LVEF) of ≥10% to an absolute value of <50%; 6-min walk test distance; and changes in cardiac biomarkers. Safety endpoints included renal dysfunction and hyperkalemia.

Assuming a mean decline in average E′ of 2.895 cm/s at 6 months and SD of 2.07 cm/s in the placebo group (1), and assuming a clinically relevant treatment effect of 50%, with a power of 0.80 and a 2-sided type I error of 0.05, 35 patients needed to be analyzed in each arm of the study. We aimed to randomize 39 patients to each arm.

TABLE 1 Baseline Characteristics of Study Group

	Eplerenone (n = 22)	Placebo (n = 22)
Age, yrs	53.9 ± 2.0	49.1 ± 12.8
Body mass index, kg/m^2	27.9 ± 7.9	27.1 ± 8.9
Comorbidities		
Coronary artery disease	0 (0)	0 (0)
Cardiomyopathy or HF	0 (0)	0 (0)
Hypertension	7 (31.8)	2 (9.1)
Diabetes	3 (13.6)	2 (9.1)
Smoking (current or former)	5 (22.7)	5 (22.7)
Cardiac medications at baseline		
Beta-blocker	1 (4.5)	0 (0)
ACE inhibitor or ARB	5 (22.7)	1 (4.5)
Diuretic agent	3 (13.6)	2 (9.1)
Baseline BNP, ng/l	28.5 (14, 36)	31.0 (9, 53)
Baseline echocardiographic measurements		
LVEF, %	63.2 ± 3.9	64.4 ± 4.2
Average E′, cm/s	9.4 ± 3.0	10.4 ± 2.9
Septal E′, cm/s	8.0 ± 2.6	9.2 ± 2.7
Lateral E′, cm/s	10.8 ± 3.6	11.5 ± 3.3
Chemotherapy protocol		
Dose-dense ACT	8 (36.4)	8 (36.4)
ACT + trastuzumab	8 (36.4)	5 (22.7)
Dose-dense ACT + trastuzumab	1 (4.5)	3 (13.6)
ACT	1 (4.5)	2 (9.1)
Other	4 (18.2)	4 (18.2)

Values are mean ± SD, n (%), or median (quartile 1, quartile 3).

ACT = Adriamycin/Cyclophosphamide/pacliTaxel; ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BMI = body mass index; BNP = B-type natriuretic peptide; HER2 = human epidermal growth factor receptor-2; HF = heart failure; LVEF = left ventricular ejection fraction.

On the basis of a pre-specified analysis after enrollment of 40 patients, the Data Safety Monitoring Board determined that the likelihood of finding a statistically significant difference in the principal outcome measure between the allocated therapies was extremely low. Assuming a SD of 1.5 cm/s (as observed in the interim data) and a mean decline in the control arm from baseline to 6 months of 0.60 cm/s (considered highly likely based on interim data), and selecting a power of 25% as sufficient to consider the continuation of the study, a treatment effect of nearly 80% would need to be observed to reach the desired power. This was not achieved at the time of the interim analysis. Accordingly, it was recommended in July 2016 that the study be terminated. All patients enrolled at that point completed 6-month follow-up; no additional patients were randomized.

The primary outcome, change in E'_{avg} at 6 months, was compared between the treatment arms using analysis of covariance, adjusting for baseline E'_{avg}. Linear regression was used to test for interaction between trastuzumab status and treatment arm. Proportions of subjects developing worsening diastolic and systolic function at 6-month follow-up were compared between treatment arms using chi-square tests. The remainder of secondary outcomes were compared using analysis of covariance, adjusting for corresponding baseline measures. Values for the primary outcome are presented as unadjusted differences with 95% confidence intervals (CIs), but p values are presented are those adjusted for baseline E'_{avg}. Baseline characteristic and other result values are presented as counts with percentages, mean ± SD, or median (quartile 1, quartile 3). Data were analyzed using SPSS software version 21 (IBM Corp., Armonk, New York).

Between June 2014 and June 2016, 44 patients were randomized. Three patients in the placebo arm withdrew from the study after randomization but before the end of chemotherapy and were not included in the final analysis. None of the withdrawals were attributed to study drug adverse effects. Median dose of study drug achieved was 50 mg daily.

The 2 groups were well matched in baseline demographic and clinical characteristics (Table 1). There were no significant differences between groups in any baseline echocardiographic parameter. All patients had normal LV systolic function; 6 patients (27.3%) in the eplerenone group and 3 patients (13.6%) had mild or moderate diastolic dysfunction at baseline.

Tumor characteristics were also well matched. Nine patients (40.9%) in the eplerenone group and 8 patients (36.4%) in the placebo group received trastuzumab. Eleven patients (50%) in each group underwent mastectomy, and the remainder underwent lumpectomy. Twenty-one (95.5%) patients in each group underwent radiation therapy after chemotherapy.

The primary outcome, mean change in E'_{avg}, was −1.01 cm/s (95% CI: −1.89 to −0.13) in the eplerenone group and −0.49 cm/s (95% CI: −1.16 to 0.18) in the placebo group (unadjusted values; adjusted p = 0.12). There were no significant between-group differences in the mean change in any secondary outcome measure of diastolic function, including E'_{septal}, $E'_{lateral}$, E/E′, E/A, or left atrial volume index, or in any measure of systolic function or chamber size, including LVEF and LV end-diastolic dimension, after adjusting for baseline values. The average change in LVEF from baseline to 6 months was −3.5% (95% CI: −6.1 to −0.9) in the eplerenone group and −2.0% (95% CI: −4.2 to 0.2) in the placebo group.

Three patients (13.6%) in the eplerenone group and 1 patient in the placebo group (5.3%) experienced worsening of diastolic function of ≥1 ASE grade between baseline and 6 months (p = 0.601). Six patients

(27.3%) in the eplerenone group and 1 patient (5.3%) in the placebo group experienced a decline in LVEF of at least 10% ($p = 0.099$). Protocol-defined systolic dysfunction occurred in 2 patients (9.1%) in the eplerenone group and no patients in the placebo group ($p = 0.490$). There was no significant interaction identified between treatment group and trastuzumab status on the outcomes of change in E'_{avg} or LVEF. The mean change in systolic blood pressure from baseline to end of study was -9.1 ± 19.8 mm Hg and 0.7 ± 13.9 mm Hg in the eplerenone and placebo groups, respectively ($p = 0.076$). There was no association between change in systolic blood pressure and the primary endpoint.

There was no significant between-group difference in change in 6-min walk test distance from baseline to 6 months, mean change in B-type natriuretic peptide or troponin from baseline to chemotherapy cycle 2 or 3, or proportion of patients with B-type natriuretic peptide or troponin above the upper limit of normal.

Adverse events were rare and not significantly more likely to occur in patients receiving eplerenone compared with placebo. No patients experienced serum potassium ≥5.5 μmol/l. One patient in the placebo group had a diagnosis of possible anthracycline-related myonecrosis on the basis of elevated troponin without change in LV function. No cases of symptomatic heart failure occurred.

In this randomized study of women receiving anthracycline-based adjuvant chemotherapy for breast cancer, concomitant administration of eplerenone did not appear to have a significant impact on study-defined diastolic function at 6 months compared with placebo. Furthermore, eplerenone did not significantly affect the change in other measures of diastolic or systolic function or reduce the risk of worsening diastolic or systolic function. Interestingly, we noted a nonsignificant trend toward a greater incidence of worsening diastolic and systolic function as binary outcomes. We attribute these findings to chance (in the context of a small sample size), and to marginally worse baseline measures of systolic and diastolic function in the eplerenone group, which may have increased the chances of crossing the thresholds to meet the categorical endpoints of worsening systolic and diastolic function.

The lack of observed effect may be attributable to a lack of statistical power. We were surprised by the small change in E'_{avg} in the study cohort; compared with the group in the study used to derive our sample size (1), our group had similar ages and chemotherapy doses and a higher prevalence of risk factors for cardiotoxicity. In any event, this unexpectedly low magnitude of change reduced the power of our study to detect between-group differences. Further, eplerenone may not have been pre-administered for a sufficient duration; previous preclinical and clinical studies demonstrating efficacy of MRAs with anthracyclines started eplerenone 5 and 7 days earlier, respectively.

To our knowledge, this is the first clinical trial of eplerenone in this population. Animal studies of eplerenone during anthracycline therapy have borne conflicting results (5,6). In a recent clinical study, systolic function and diastolic function were better preserved in patients receiving spironolactone versus placebo during anthracycline chemotherapy (7). The 2 studies differed in MRA used, timing of evaluations relative to chemotherapy administration, and chemotherapy regimens administered, and these variations may explain the different findings.

Unexpectedly low frequency and severity of cardiotoxicity have been observed in other trials of anthracycline cardioprotection (8,9). The magnitude of decline in LVEF in our study and other recent trials was dramatically different from that reported in many older studies (10), thus suggesting that cardiotoxicity risk may be improving in the context of contemporary oncology care. Teams designing future studies of cardioprotective agents should bear this in mind; adequately powered trials may require study groups with high-risk baseline characteristics. Future research should also aim to identify high-risk patients most likely to benefit from prophylaxis.

In addition to the low statistical power, a notable limitation of our study is that changes in global longitudinal strain, an emerging marker of anthracycline cardiotoxicity (2), were not measured because strain imaging was not yet part of standard care at the time of trial design. It is also possible that eplerenone was not administered for a sufficient duration before anthracycline exposure; previous pre-clinical and clinical studies demonstrating efficacy of MRAs with anthracyclines started eplerenone 5 and 7 days earlier, respectively (6,7). Finally, the relatively short duration of follow-up is a limitation of the study; different results may have been observed over a longer duration.

In conclusion, concomitant administration of eplerenone for 6 months was not associated with significant differences in systolic or diastolic function compared with placebo in patients with early or locally advanced breast cancer treated with anthracycline-based chemotherapy. We cannot exclude the possibility that a difference would have been observed in a larger study or with a different group of patients. Future studies should focus on

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high-risk patients who may be more likely to derive benefit from cardioprotective agents.

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Exercise Attenuates Cardiotoxicity of Anthracycline Chemotherapy Measured by Global Longitudinal Strain

Anthracycline-based chemotherapy (AC) is a common treatment for patients with breast cancer and has been associated with a dramatic improvement in breast cancer survivorship. Among patients with early-stage breast cancer, cardiovascular diseases represent the most common cause of mortality, and there is a growing emphasis on strategies for minimizing the toxic effects of breast cancer treatments on the cardiovascular system (1).

The primary therapeutic approach for preventing heart failure following anthracycline exposure is to intervene with heart failure pharmacotherapy in patients with cardiac dysfunction (1,2). However, patients may be less responsive to this approach if dysfunction is detected late (3), and so there is interest in primary preventive approaches. Exercise training has been proposed as 1 such approach (4) because it is safe, inexpensive, and already recommended as a strategy for counteracting other adverse effects of cancer treatment. However, little is known about whether exercise training can effectively counteract the cardiotoxic effects of AC.

Cardiac magnetic resonance (CMR) is an increasingly available imaging method for assessing cardiac function. The excellent image resolution makes CMR assessment of ventricular volume and function the gold standard noninvasive technique, and sequences such as T_1 mapping may allow early detection of chemotherapy-related inflammation, edema, and fibrosis.

In this study, we evaluated native T_1 mapping at 3-T using inversion recovery (ShMOLLI) and saturation recovery (SASHA) techniques and measured global longitudinal strain (GLS) using feature tracking of cine images, before and after completion of AC-based chemotherapy. A subset of the study group underwent exercise training. We hypothesized that: 1) anthracyclines would increase myocardial inflammation (T_1 mapping) and impair systolic function measured by GLS; and 2) exercise training would attenuate these changes.

This was a single-center, nonrandomized clinical trial. All research was performed at the Baker Heart and Diabetes Institute, Melbourne, Australia, between May 2016 and December 2017. The experimental procedures were explained to all participants,