Journal of Cancer and Tumor International

12(3): 1-10, 2022; Article no.JCTI.87519
ISSN: 2454-7360

Prevention of Adjuvant Treatment Induced Cardiotoxicity in Egyptian Breast Cancer (BC) Patients: A Randomized Prospective Study

Azza M. Adel [a*], Niven M. Gado [a], Dina Ragab [a], Yasmin Abdelrazek Ali [b], Ahmed Samir [c] and Hagar Ibrahim [a]

[a] Clinical Oncology Department, Faculty of Medicine, Ain Shams University, Egypt.
[b] Cardiology Department, Faculty of Medicine, Ain Shams University, Egypt.
[c] Radiology Department, Faculty of Medicine, Ain Shams University, Egypt.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JCTI/2022/v12i330177

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/87519

Original Research Article

Received 20 March 2022
Accepted 31 May 2022
Published 03 June 2022

ABSTRACT

Background: Adjuvant Anthracyclines Chemotherapy (ANTC) and trastuzumab have been documented to prolong survival in patients with breast cancer (BC). However, these drugs are also well known to induce left ventricular systolic dysfunction (LVSD). Multiple studies have shown that angiotensin converting enzyme inhibitors (ACEIs) and beta blockers (BBs) can prevent LVSD among women with BC.
Objectives: We aimed to prospectively evaluate the efficacy of enalapril (ACEI) and carvedilol (BB) in preventing the ANTC ± trastuzumab induced LVSD, in patients with non-metastatic BC.
Patients and Methods: We randomized 126 patients with non-metastatic (M0) BC, who were scheduled to be treated with ANTC ± trastuzumab into the intervention group (group 1; n = 63), which received enalapril and carvedilol or the control group (group 2; n = 63), which did not receive enalapril or carvedilol. To evaluate left ventricular (LV) systolic and diastolic functions the conventional echocardiography (ECHO) and cardiac magnetic resonance imaging (CMR) were performed at baseline, after 3 therapy cycles, and at 1-year follow-up. The secondary endpoint was designed to detect the incidence of a decrease in left ventricular ejection fraction (LVEF) ≥ 10%, heart failure (HF), LVSD (defined as LVEF<45%) or deterioration in LV diastolic function.
Results: In the intervention group, 58 patients had 3 cycles ANTC, 6 patients received 6 cycles ANTC, and 12 patients received trastuzumab. In the control group, 47 patients had 3 cycles ANTC,

**Corresponding author: Email: azzaelkhateeb@gmail.com;*

16 patients were given 6 cycles ANTC and 18 patients received trastuzumab (as per the guidelines *issued by breast clinic in the department of clinical oncology, faculty of medicine, Ain Shams University*) for adjuvant and neoadjuvant chemotherapy in early breast cancer).
After 3 ANTC cycles, LVEF did not change in the intervention group, but decreased by M-mode in the control group (p-value: 0.03), which was associated with statistically significant deterioration of LV diastolic function. At 1 year follow-up, while no change was observed in LVEF in group 1, there was a decrease in LVEF by CMR in group 2 (65.78% at baseline, 61.48% at 1 year; p-value: 0.04 8).
Conclusion: Combined prophylaxis with enalapril and carvedilol may prevent LVSD in patients with non-metastatic BC treated with anthracycline-containing chemotherapy ± trastuzumab. However, the clinical relevance of this strategy should be confirmed in the future, large-scale randomized studies.

Keywords: Cardioprotection; breast cancer (BC); cardiotoxicity; anthracyclines; trastuzumab.

1. INTRODUCTION

Anthracyclines, taxanes and trastuzumab which are largely used in the adjuvant setting of cancer breast are associated with remarkable improvement of both disease-free and overall survival [1]. However, they are known for causing cardiac dysfunction both symptomatic and asymptomatic [2,3]. Risk factors for anthracyclines induced cardiotoxicity include prior or current history of coronary artery disease, cardiac dysfunction, hypertension, and age. The cumulative incidence of cardiac toxicity peaks at 1 year after anthracycline therapy [4,5].

The early detection of anthracycline induced left ventricular dysfunction is important to detect early cardiac damage thus allowing regimen modifications and early treatment. The diagnostic approach to detect cardiac damage depends primarily on the estimation of left ventricular ejection fraction (LVEF). Conventional echocardiography provides information on LV structure and assesses both systolic and diastolic functions [6]. Although 2-dimensional (2D) echocardiography can detect relatively significant decreases in LVEF (e.g., from 60% to 40%), smaller drops as from 54% to 48% are more difficult to identify with a high degree of certainty [7]. This limitation is addressed by 3D methods to detect the small changes in LVEF [7]. The cardiac magnetic resonance (CMR) imaging modality can give accurate and reproducible assessment of many parameters including the diastolic and systolic functions of both ventricles [8]. Cardiac Magnetic Resonance imaging (CMR) is recognized by the American College of Cardiology/American Heart Association as a method to detect cardiovascular CV dysfunction after cancer treatment [9].

Both beta blockers (BBs) and Anti Converting Enzyme Inhibitors (ACEIs) have been shown to slow the progression and to prevent heart failure in patients with LVSD whether due to infarction or anthracycline-induced cardiomyopathy [2,9,10]. Administration of both ACEIs and BBs has additive beneficial effects in patients with LVSD [9].

The aim of this prospective randomized study was to evaluate the efficacy of enalapril (ACEI) and carvedilol (BB) in preventing the anthracyclines chemotherapy (ANTC) ± trastuzumab induced systolic dysfunction (LVSD defined as LVEF < 45%) as well as diastolic dysfunction in patients with non-metastatic (M0) breast cancer. For this evaluation we used 2D echocardiography and CMR parameters. The secondary endpoint was detecting the incidence of decrease in (LVEF) ≥ 10%, heart failure (HF), or deterioration in LV diastolic function.

2. PATIENTS AND METHODS

This is a phase III, randomized controlled trial conducted at the Clinical Oncology and nuclear medicine department, Cardiology department, and radiodiagnosis department, Faculty of Medicine, Ain-Shams University. The study was approved by the Institutional Review Board of Faculty of Medicine, Ain-Shams University. All the patients gave their written consent.

2.1 The Inclusion Criteria

age from 18 to 75 years old, non-metastatic disease, adjuvant or neoadjuvant ANTC ± Trastuzumab indicated, normal baseline cardiac function including sinus rhythm and echocardiographic LVEF ≥50%.

2.2 Exclusion Criteria

Cardiac insult (congestive heart failure, myocardial infarction,) Electrocardiogram (ECG) abnormalities (atrioventricular block or sinus bradycardia (heart rate < 60 beats/min), atrial fibrillation), echocardiography findings (LVEF <50%, significant valvular or myocardial disease) ,ongoing or expected need to be treated with ACEI or beta-blockers, allergy to ACEI, or beta-blockers, systolic blood pressure < 90 mm Hg, need to be treated with a class I antiarrhythmic drug, renal failure (glomerular filtration rate < 30 ml/h/m²), hepatocellular insufficiency or grade III to IV increase of liver enzymes (any ALT increase by > 5 times ULN or any increase of 100 U/L from baseline).

2.3 Randomization

The patients were randomized in a 1:1 ratio to receive (the intervention group, group 1) or not receive (the control group, group 2) enalapril and carvedilol. Participants in each group were 63 patients.

2.4 Study Treatment

Anthracyclin chemotherapy (ANCT) was repeated every 21 days in cycles according to the recommendations of the breast unit at clinical oncology department. Adriamycin was given at a dose of 50mg/m² (FAC regimen) or 60mg/m² (AC regimen). Epirubicin was administered at a dose of 100mg/m². *Trastuzumab* was started when indicated according to the guidelines of the breast clinic. As regards carvedilol and enalapril we followed the same doses and schedules of the OVERCOME trial (Bosch et al 2013) in combination throughout the anthracycline chemotherapy cycles with dose titration and stopped after finishing the anthracyclines [12]. Both enalapril and carvedilol were started at least 24 hours before the first chemotherapy cycle. The initial dose of enalapril was 2.5 mg twice daily in normotensive patients (1.25 mg in patients with systolic blood pressure (SBP) between 90 mm Hg and 100 mm Hg), then was gradually increased every 7 to 10 days under close supervision to 5 mg and 10 mg twice daily if SBP persistently remained >90 mm Hg. In case of hypotension, the dose was reduced to the closest level or stopped, and the lowest dose was resumed when SBP persistently remained >90 mm Hg. The initial dose of carvedilol was 3.125 mg twice and increased gradually every 7 to 10 days to 12.5 mg twice daily in the absence of clinical signs of congestive heart failure, sinus bradycardia <60 beats/min or any degree of atrioventricular block. In the case of hypotension or bradycardia, the dose was also reduced to the closest level. Cardioprotective drugs were stopped if significant side effects developed BP ≤ 90/50, HR ≤ 55 beat per minute (bpm).

Conventional echocardiography was done at baseline, after 3 cycles and after 1 year of follow-up. Patients who received trastuzumab had echocardiography done at baseline and every 3 cycles. To avoid bias, echocardiography was performed by the same independent experienced cardiologist who was blinded to the patient's allocated treatment group. The following parameters were assessed; LVEF (by M- mode and modified Simpson method), LV diastolic function (using LV inflow E and A peak diastolic velocities, E deceleration time, E/A ratio), Interventricular relaxation time (IVRT), lateral mitral annulus motion by tissue Doppler (Em, E/Em), diastolic dysfunction grade, LA volume, end diastolic and systolic volumes (EDV, ESV), end diastolic and systolic diameters (EDD, ESD).

Cardiac magnetic resonance imaging was performed at baseline, after 3 months and after 1 year of follow-up. It was carried out with a 1.5 T Acheiva MRI machine (Philips) using dedicated phased array 16 channel cardiac coil. Global LVEF and diastolic function including ESV and EDV were assessed using standard steady-state free precision Cine white blood imaging (SSFP).

Study endpoints: The primary endpoint was to measure the change in global LVEF as measured by echocardiography and CMR imaging, after 3 cycles, and one year of treatment. The secondary endpoint was to detect the incidence of absolute decrease in LVEF ≥ 10%, heart failure, significant LVSD (LVEF < 45%) or deterioration in LV diastolic function.

2.5 Statistical Analysis

Data were collected, revised, coded, and entered to the Statistical Package for Social Science (IBM SPSS) version 20 for Windows (SPSS, Chicago, IL, USA). Qualitative data were presented as numbers and percentages while quantitative data (age, weight, height, BSA, cumulative ANTC doses, echocardiographic, and CMR parameters) were presented as mean, standard deviation and ranges. The comparison between the two groups with qualitative data was done using Chi-square test and/or Fischer test was used instead of chi-square test when the expected count in any cell was < 5. The comparison between the two groups regarding

quantitative data with parametric distribution was done using the independent *t*-test while comparison between two paired groups regarding quantitative data with parametric distribution was done using paired *t*-test. Spearman correlation coefficients were used to assess the correlation between two quantitative parameters in the same group.

The confidence interval was set up to 95% and the margin of error accepted was set to 5%. So, the *p*- value was considered significant as follows $p>0.05$ is non-significant, $p< 0.05$ is significant and $p< 0.01$ is highly significant.

3. RESULTS

Between May 2014 and December 2015, 126 were included in the study. The two study groups were well balanced as regards the baseline clinical characteristics (Table 1).

In the intervention group 58 patients had 3 cycles ANTC, 6 patients received 6 cycles ANTC, and 12 patients received trastuzumab. Whereas in the control group 47 patients had 3 cycles ANTC, 16 patients were given 6 cycles ANTC and 18 patients received trastuzumab. In the intervention group 31/63 of patients (49.2%) versus 20/63 patients (31.7%) in the control group were followed up to one year after ANTC.

In the intervention group, the maximum administered dose of enalapril and carvedilol for every patient was 7.5 ± 4 mg/day and 9.7 ± 3.2 mg/day respectively. The duration of administration of enalapril and carvedilol was 65.46 ± 33.7 days and 70.37 ± 29.8 days respectively. For patients who received trastuzumab, the mean duration of enalapril and carvedilol was 313 ± 197 days.

Baseline echocardiography and baseline CMR were comparable.

3.1 After 3 months follow up: no changes were observed in the intervention arm (Table 2&Table 3). In the control group there was a statistically significant decrease in the EF by M-mode (*p*0.039) (Table 2), and in diastolic function grades (p 0.037). Regarding the diastolic function grades, data were not reported in 2 patients and 7 patients of both groups respectively (Table 3).

Table 1. Baseline clinical characteristics in both groups

		Group I (intervention)	Group II (control)	P-value
		N = 63	N = 63	
Age	Mean ± SD	47.17 ± 10.16	49.59 ± 11.22	0.208
	Range	27 – 67	24 – 73	
Diabetes mellitus	Negative	54 (85.7%)	57 (90.5%)	0.409
	Positive	9 (14.3%)	6 (9.5%)	
BSA	Mean ± SD	1.84 ± 0.16	1.84 ± 0.15	0.968
	Range	1.4 – 2	1.47 – 2	
Laterality	Bilateral	2 (3.2%)	1 (1.6%)	
	Lt	31 (49.2%)	27 (42.9%)	0.608
	Rt	30 (47.6%)	35 (55.6%)	
Surgery	BCS	24 (38.1%)	24 (38.1%)	
	MRM	27 (42.9%)	28 (44.4%)	0.970
	Negative	12 (19.0%)	11 (17.5%)	
Stage	I	2 (3.2%)	2 (3.2%)	
	II	21 (33.3%)	24 (38.1%)	0.957
	III	28 (44.4%)	26 (41.3%)	
	LABC	12 (19.0%)	11 (17.5%)	
ER	Negative	23 (36.5%)	16 (25.4%)	0.177
	Positive	40 (63.5%)	47 (74.6%)	
PR	Negative	29 (46.0%)	22 (34.9%)	0.204
	Positive	34 (54.0%)	41 (65.1%)	
HER-2	Negative	51 (81.0%)	45 (71.4%)	0.209
	Positive	12 (19.0%)	18 (28.6%)	
DVT	Negative	60 (95.2%)	58 (92.1%)	0.465
	Positive	3 (4.8%)	5 (7.9%)	

BSA: basal surface area, LABC: locally advanced breast cancer, ER: estrogen receptor, PR: progesterone receptor; HER-2: human epidermal receptor, DVT: deep venous thrombosis

Table 2. Imaging evaluation after 3 cycles of anthracyclines chemotherapy in the intervention and control groups (n = 63 each)

	Intervention group after 3 cycles anthracyclines			Control group after 3cycles anthracyclines		
Echo parameters	**Baseline**	**After 3 cycles**	**p-value**	**Baseline**	**After 3 cycles**	**p-value**
	Mean ± SD	**Mean ± SD**		**Mean ± SD**	**Mean ± SD**	
LVEF S	63.89 ± 4.59	62.65 ± 4.36	0.098	64.14 ± 4.87	63.14 ± 4.96	0.231
LVESV	34.90 ± 9.2	35.45 ± 9.03	0.735	38.25 ± 11.61	36.42 ± 9.32	0.331
LVEDV	98.43 ± 23.44	93.80 ± 23.15	0.263	105.31 ± 27.15	96.61 ± 22.44	0.075
EF M	64.35 ± 4.21	63.59 ± 3.49	0.219	64.84 ± 4.82	63.42 ± 4.89	0.039
EDD	5.22 ± 4.45	4.69 ± 0.47	0.366	4.72 ± 0.48	4.72 ± 0.49	0.971
ESD	3.01 ± 0.30	3.58 ± 3.75	0.238	3.03 ± 0.41	3.07 ± 0.39	0.398
CMR parameters						
CMR EF	66.18 ± 6.40	66.22 ± 7.24	0.959	69.14 ± 6.23	67.06 ± 5.38	0.119
CMR EDV	99.35 ± 25.36	94.59 ± 29.68	0.245	86.54 ± 33.00	76.72 ± 28.46	0.211
CMR ESV	41.80 ± 15.20	39.73 ± 16.86	0.370	34.86 ± 16.49	31.33 ± 16.43	0.385

LVEF S: LV EF by Simpson, LVESV: LV end systolic volume, LVEDV: LV end diastolic volume, EF M: EF by M mode, EDD: end diastolic diameter, ESD: end systolic diameter, CMR: cardiac magnetic resonance

Table 3. Comparison of diastolic dysfunction after 3 cycles of chemotherapy in both groups

Diastolic grade	**Group 1 before chemotherapy**		**Group 1 after 3 cycles**		***P*-value**
	Pt. no.	**baseline diastolic grade**	**Pt. no.**	**diastolic grade**	0.313
NR	0	0%	2	3.20%	
Normal	12	19%	18	28.6%	
1	40	63.5%	35	55.6%	
2	10	16%	8	12.7%	
3	1	1.6%	0	0.00%	
	Group 2 before chemotherapy		**Group 2 after 3 cycles**		
NR	0	0%	7	11.1%	**0.037**
Normal	17	27 %	13	20.6%	
1	42	66.7%	34	54%	
2	4	6.3%	9	14.3%	
3	0	0.00%	0	0.00%	

Table 4. Imaging evaluation 1 year after chemotherapy in the intervention and control groups

	Intervention group 1 year post-chemotherapy			Control group 1 year post-anthracyclines		
Echo parameters	**Baseline**	**After 1 year**	**p-value**	**Baseline**	**After 1year**	**p-value**
	Mean ± SD	**Mean ± SD**		**Mean ± SD**	**Mean ± SD**	
LVEF S	64.75 ± 4.51	62.88 ± 4.15	0.157	63.83 ± 5.57	62.08 ± 3.48	0.312
LVESV	35.91 ± 9.09	38.61 ± 13.26	0.368	37.33 ± 13.08	38.42 ± 8.48	0.768
LVEDV	104.71 ± 21.73	104.38 ± 29.48	0.958	104.17 ± 32.68	103.08 ± 26.47	0.905
EF M	65.12 ± 4.29	63.27 ± 3.73	0.110	63.92 ± 3.88	62.77 ± 2.89	0.282
EDD	4.56 ± 0.35	4.79 ± 0.37	**0.005**	4.75 ± 0.52	4.64 ± 0.51	0.565
ESD	2.93 ± 0.26	3.15 ± 0.32	0.001	3.12 ± 0.38	3.12 ± 0.18	1.000
CMR parameters						
EF	65.92 ± 5.90	64.90 ± 5.79	0.507	65.78 ± 5.70	61.48 ± 3.29	0.048
EDV	107.15 ± 20.34	86.12 ± 22.12	**0.002**	93.80 ± 32.81	78.85 ± 31.75	0.108
ESV	45.36 ± 10.66	39.14 ± 13.95	0.095	41.79 ± 16.65	39.77 ± 25.44	0.799

LVEF S: LV EF by Simpson, LVESV: LV end systolic volume, LVEDV: LV end diastolic volume, EF M: EF by M mode, EDD: end diastolic diameter, ESD: end systolic diameter, CMR: cardiac magnetic resonance

Table 5. Comparison of diastolic grades in both groups who achieved 1 year follow-up after chemotherapy

Diastolic grade	**Baseline grades of intervention group patients who achieved 1 year follow-up (n =31)**		**After 1 year**		***p*-value**
	Pt. no. (31)	%	**Pt. no.**	%	
NR	3	9.7%	3	9.6%	
Normal	6	19.4%	7	25.0%	0.856
1	18	58. %	19	67.9%	
2	4	12.9%	2	7.1%	
	Baseline grade of control group patients who achieved 1 year follow-up (n = 20)		**After 1 year**		***p*-value**
	Pt. no. (20)	%	**Pt. no.**	%	0.835
NR	4	20.0%	4	20.0%	
Normal	4	20%	2	12.5%	
1	9	45%	10	62.5%	
2	3	15%	4	25.0%	

NR: not reported

3.2 At 1 year of follow-up

Thirty one out of 63 patients in group I compared to 20 out of the 63 patients of group II were followed for one year. While no change was observed in LVEF by any tool (Modified Simpson method, M-mode or CMR) in the intervention arm (Table 4), there was a statistically significant decrease in EF by CMR in the control arm (baseline EF 65.78%, 1 year 61.48%, *p*0.048). The end diastolic volume (EDV) in the intervention group was reduced as detected by both the echocardiography and CMR (baseline 107.15 ml/m2, after 1 year 86.12 ml/m2, *p* 0.002) as shown in table [4]. Similarly, there was improvement of diastolic function grades although not statistically significant **(**Table 5). On the other hand, the control arm, showed deterioration of diastolic function grades (Table 5).

3.3 Cardiac Events during the Study Period (secondary endpoint)

No cases were detected with heart failure or with final EF < 45 % in either group. Compared to controls, the intervention group had a statistically significant lower incidence of decrease EF ≥10 % after finishing ANTC (1.9% vs. 12.5%, *p*= 0.04) (Table 6) and at 1 year follow-up (3.6% vs. 18.8%, *p* 0.09) (Table 7).

4. DISCUSSION

Cardiotoxicity from anthracycline therapy is defined as a decrease of LVEF from ≥5% to <55% associated with heart failure symptoms or an asymptomatic decline of LVEF ≥10% to <55%. Similarly, the diastolic parameters are markers for early cardiomyopathy [11].

Randomized clinical trials studied BBs, ACEIs, angiotensin receptors blockers (ARBs) for primary prevention of anthracycline induced cardiotoxicity [12,13,10]. These trials showed that LVEF dropped significantly after chemotherapy in placebo or control groups, but not in intervention groups. Despite these declines, LVEFs remained >50%.

Table 6. Incidence of EF decrease ≥ 10% after ANTC by echocardiography and CMR in both groups after 3 months

Evaluation method		Group I		Group II		*P*-value
		No.	%	No.	%	
≥ 10 % decrease Modified Simpson	**Total pt. no./63**	**57**		**54**		0.452
	Negative	53	93.0%	48	89%	
	Positive	4	7.0%	6	11.1%	
≥ 10 % decrease M mode	**Total pt. no./63**	**60**		**54**		0.498
	Negative	59	98.3%	52	96.3%	
	Positive	1	1.7%	2	3.7%	
≥ 10 % decrease CMR	**Total pt. no./63**	**53**		**32**		0.044
	Negative	52	98.1%	28	87.5%	
	Positive	1	1.9%	4	12.5%	

Table 7. Incidence of EF decrease ≥ 10% at 1 year of follow-up by echocardiography and CMR In both groups

Evaluation method		Group I		Group II		*P*-value
		No.	%	No.	%	
≥10 % decrease Modified Simpson	**Total pt. no./63**	**28**		**16**		
	Negative	27	96.4%	13	81.2%	0.092
	Positive	1	3.6%	3	18.8%	
≥10 % decrease M-mode	**Total pt. no./63**	**28**		**16**		
	Negative	25	89.3%	14	87.5%	0.858
	Positive	3	10.7%	2	12.5%	
≥10 % decrease CMR	**Total pt. no./63**	**24**		**10**		
	Negative	24	100.0%	9	90.0%	0.116
	Positive	0	0.0%	1	10.0%	

We conducted this randomized controlled prospective study of the protective role of carvedilol and enalapril given simultaneously in non- metastatic breast cancer patients treated with anthracycline chemotherapy with or without trastuzumab.

This current study

1) added to the bulk of evidence which supports the possible role of ACEIs and BBs in primary prevention of cardiotoxicity of anthracyclins.
2) Carvedilol and enalapril prevented the drop of LVEF after 3 cycles of ANTC in the intervention group by echocardiography.
3) Carvedilol and enalapril protected the LVEF at one year of follow-up in the intervention group by CMR.
4) At one year follow-up the intervention group had lower incidence of reduced EF ≥10% as detected by CMR compared to the control group.
5) At one-year post- chemotherapy the diastolic function grades improved in the intervention group while deteriorated in the control group.

Our study results agreed with the suggested cardioprotective role of ACEIs and BBs, by sparing the LVEF in the intervention arm after 3 cycles ANTC (*p*0.098) and at 1 year follow-up (*p*0.157) after chemotherapy, whereas the control group patients had a statistically significant decrease in the (EF) by M-mode (*p* 0.03), also there was a statistically significant decline of the LVEF in the control group at 1-year follow-up that was detected only by CMR (*p* 0.048).

Our results are in agreement with Radulesc et al 2013 results where the authors prospectively assigned different types of cancer patients into a study group (n=68) who received epirubicin and perindopril (ACI) or to a control group (n= 68) who received epirubicin but no ACI. By the end of chemotherapy, the LVEF was less changed in the study group compared to the control group. The study also documented a significant deterioration of LV diastolic dysfunction in both groups at the completion of chemotherapy [14].

Bosch et al 2013 tested in a randomized controlled trial the efficacy of combined enalapril and carvedilol to prevent anthracycline-induced cardiotoxicity in 90 patients with hematologic malignancies. The patients were randomized to a group receiving enalapril and carvedilol or to a control group. After 6 months, no change of LVEF was observed in the intervention group; conversely LVEF significantly decreased in the control group (*p* 0.035) [12].

The PRADA trial, (Prevention of Cardiac Dysfunction During Adjuvant Breast Cancer Therapy) focused on exploring the preventive role of candesartan (ARB) and metoprolol (BB) in 120 patients diagnosed with early breast cancer, The authors showed that the decline in LVEF from the baseline to the end of the study was 2.6% (95% CI 1.5, 3.8) in the placebo group and 0.8 (95% CI 20.4, 1.9) in the candesartan group in the intention-to-treat analysis (P-value for between-group difference: 0.026), while no effect of metoprolol on the overall decline in LVEF was detected [15].

These findings are in agreement with Kaya et al 2013 [13] prospective, double-blind, randomized trial on 45 breast cancer patients who received anthracyclines and prophylactic BBs (nebivolol) 5 mg daily in 27 patients and placebo in 18 patients. The placebo group also had lower LVEF by echocardiography than the nebivolol group (57.5±5.6% vs.63.8±3.9%, p=0.01) at 6-month. The authors concluded that prophylactic nebivolol may protect the myocardium against AIC in breast cancer. Similarly, Elitok et al 2014 [16] concluded in their trial that carvedilol has a protective effect against the ANTC. Bosch et al 2013, [12] and el shitany et al 2012 [17] who both studied carvedilol in patients receiving anthracyclines did not find differences in LV indices of diastolic function.

Meta-analysis was carried out by Yun et al [18] which aimed to determine the efficacy of BBs and ACEIs in preventing the early onset of anthracyclines- induced LVD and cardiac events. The authors concluded that both BBs and ACEIs lead to better LVEF preservation especially among patients treated with high doses of anthracyclines.

In the present study, after 3 cycles of ANTC the carvedilol and enalapril prevented the reduction of LVEF by echo in the intervention group. In the limited number of patients who completed one year follow-up after ANTCs in this trial, we did not detect HF or EF < 45% in either arm. Compared to the control group, the intervention group demonstrated a lower incidence of reduced EF ≥ 10% by CMR (1.9% vs. 12.5%, *p* 0.04) after completion of ANTCs and at one year follow-up (3.6% vs. 18.8%, *p* 0.09). Our findings are in agreement with the OVERCOME trial where the authors reported a lower incidence of HF or significant LVSD.

5. CONCLUSION

The concomitant use of ACIs and BBs seems to have a protective effect against anthracyclines induced-cardiotoxicity. Our study and similar other trials emphasize the need for early and continuous close collaboration between cardiologists and oncologists to balance the risks and benefits of cardiotoxic anti-cancer agents in patients with BC. Early identification of patients at high risk for cardiotoxicity is crucial, but it is still inadequate, with using the current methods (e.g., LVEF and cardiac biomarkers).

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

As per international standard or university standard, patients' written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Smith LA, Cornelius VR, Plummer CJ, et al. Cardiotoxicity of anthracycline agents for the treatment of cancer: Systematic review and metaanalysis of randomised controlled trials. BMC Cancer. 2010;10:337.
2. Cardinale D, Colombo A, Lamantia G, et al. Anthracycline-induced cardiomyopathy: Clinical relevance and response to pharmacologic therapy. Jam Coll Cardiol. 2010;55:213-20.
3. Suter TM and Ewer MS. Cancer drugs and the heart: importance and management. Eur Heart J; 2012.
4. Perez EA, Koehler M, Byrne J, et al. Cardiac safety of lapatinib: pooled analysis of 3689 patients enrolled in clinical trials. Mayo Clin Proc. 2008; 83:679–86.
5. Tan-Chiu E, Yothers G, Romond E, et al. Assessment of cardiac dysfunction in a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel, with or without trastuzumab as adjuvant therapy in node-positive, human epidermal growth factor receptor 2-overexpressing breast cancer: NSABP B-31. J Clin Oncol. 2005; 23:7811-9.
6. Armstrong GT, Plana JC, Zhang N, et al. Screening adult survivors of childhood cancer for cardiomyopathy: Comparison of echocardiography and cardiac magnetic resonance imaging. J Clin Oncol. 2012; 30:2876.
7. Pai VB and Nahata MC. Cardiotoxicity of chemotherapeutic agents: Incidence, treatment and prevention. Drug Saf. 2000;22:263–302.
8. Armstrong AC, Gidding S, Gjesdal O et al. LV mass assessed by echocardiography and CMR, cardiovascular outcomes, and medical practice. JACC Cardiovasc Imaging. 2012;5:837-48.
9. Hunt SA, Abraham WT, Chin MH et al; American College of Cardiology Foundation; American Heart Association. 2009 focused update incorporated into the ACC/AHA 2005 guidelines for the diagnosis and management of heart failure in adults: a report of the American College of Cardiology Foundation/ American Heart Association Task Force on Prac- tice Guidelines. J Am Coll Cardiol. 2009;53:e1–90
10. Kalay N, Basar E, Ozdogru I et al. Protective effects of carvedilol against anthracycline-induced cardiomyopathy. J Am Coll Cardiol. 2006;48:2258–62.
11. Curigliano G, Cardinale D, Suter T, et al. Cardiovascular toxicity induced by chemotherapy, targeted agents and radiotherapy: ESMO clinical practice guidelines. Annals of Oncology. 2012; 23(SUPPL. 7).
12. Bosch X, Sitges M, Rovira M, et al. Enalapril and Carvedilol to prevent chemotherapy-induced left ventricular systolic dysfunction in patients with malignant hemopathies. J Am Coll Cardiol [Internet]. 2013;61(23).

13. Kaya MG, Ozkan M, Gunebakmaz O, et al. Protective effects of nebivolol against anthracycline-induced cardiomyopathy: A randomized control study. Int J Cardiol. 2013;167(5):2306–10.
14. Radulescu D, Buzdugan E, Ciuleanu TE, et al. Can the epirubicin cardiotoxicity in cancer patients be prevented by angiotensin converting enzyme inhibitors? J BUON. 2013;18(4):1052–7.
15. Gulati G, Heck SL, Ree AH, et al. Prevention of cardiac dysfunction during adjuvant breast cancer therapy (PRADA): a 2 × 2 factorial, randomized, placebo-controlled, double-blind clinical trial of candesartan and metoprolol. Eur Heart J. 2016;022.
16. Elitok A, Oz F, Ahmet Y, et al. Effect of carvedilol on silent anthracycline-induced cardiotoxicity assessed by strain imaging: A prospective randomized controlled study with six-month follow-up. Cardiol J. 2014;21(5):509–15.
17. El-Shitany NA, Tolba OA, El-Shanshory MR, El-Hawary EE. Protective effect of carvedilol on adriamycin-induced left ventricular dysfunction in children with acute lymphoblastic leukemia. J Card Fail. 2012;18(8):607-613.
DOI:10.1016/j.cardfail.2012.06.416
18. Yun S, Vincelette ND, Abraham I. Cardioprotective role of β-blockers and angiotensin antagonists in early-onset anthracyclines-induced cardiotoxicity in adult patients: A systematic review and meta-analysis. Postgrad Med J. 2015; 91:627–633.
DOI: 10.1136/postgradmedj-2015-133535.

Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle5.com/review-history/87519