

## Review Form 1.6

Journal Name:	<a href="#">Journal of Cancer and Tumor International</a>
Manuscript Number:	Ms_JCTI_87519
Title of the Manuscript:	Prevention of adjuvant treatment induced cardiotoxicity in Egyptian breast cancer patients: a randomized prospective study
Type of the Article	Original Research Article

### General guideline for Peer Review process:

This journal's peer review policy states that **NO** manuscript should be rejected only on the basis of '**lack of Novelty**', provided the manuscript is scientifically robust and technically sound. To know the complete guideline for Peer Review process, reviewers are requested to visit this link:

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## Review Form 1.6

### PART 1: Review Comments

	Reviewer's comment	Author's comment (if agreed with reviewer, correct the manuscript and highlight that part in the manuscript. It is mandatory that authors should write his/her feedback here)
<b>Compulsory</b> REVISION comments	<p>The Manuscript: 'Prevention of adjuvant treatment induced cardiotoxicity in Egyptian breast cancer patients: a randomized prospective study' is interesting, because it addresses some common and important issues of cardio-oncology. However, it requires a revision. Suggestions for some changes are provided.</p> <p>P # 1 Title It is: Prevention of adjuvant treatment induced cardiotoxicity in Egyptian breast cancer patients: a randomized prospective study'</p> <p>It should be:</p> <p><b>Prevention of cardiotoxicity induced by adjuvant oncology treatment in Egyptian patients with breast cancer:</b> a randomized prospective study'</p> <p>Please, use the phrase: '<b>patients with breast cancer (BC)</b>' instead of: 'breast cancer patients'[this is relevant to the whole text].</p> <p>P # 1 Abstract It is: Objectives: We aimed to prospectively evaluate the efficacy of enalapril (anti converting enzyme inhibitor: ACEI) and carvedilol (beta blocker: BB) in preventing the anthracyclines chemotherapy (ANTC) ± trastuzumab induced left ventricular systolic dysfunction (LVSD) in patients with non-metastatic (M0) breast cancer. Background: Adjuvant Anthracyclin Chemotherapy (ANTC) and trastuzumab are documented to prolong survival in breast cancer patients. However, these drugs are well known to induce LVSD. Multiple studies showed that ACEIs and BBs can prevent LVSD. Patients and Methods: We randomized 126 non metastatic breast cancer patients scheduled to be treated with ANTC ± trastuzumab into an intervention group; group 1, (n= 63 patients) which received enalapril and carvedilol or to a control group which did not receive enalapril and carvedilol; group 2, (n= 63 patients). To evaluate systolic and diastolic functions conventional echocardiography and cardiac magnetic resonance imaging (CMR) were performed at baseline, after 3 cycles, and at 1 year follow-up. Secondary endpoint was detecting the incidence of decrease in left ventricular ejection fraction (LVEF) ≥ 10%, heart failure (HF), LVSD (defined as LVEF&lt;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. Whereas in the control group 47 patients had 3 cycles ANTC, 16 patients were given 6 cycles ANTC and 18 patients received trastuzumab (as per the guidelines of the breast clinic for adjuvant and neoadjuvant chemotherapy in early breast cancer). After 3 ANTC cycles, LVEF did not change in group 1, but decreased by M- mode in the control group (p-value: 0.03) associated with statistically significant deterioration of diastolic function grades. At 1 year follow-up, while no change was observed in LVEF in group 1, there was decrease in LVEF by CMR in group 2 (65.78% at baseline, 61.48% at 1 year (p value: 0.048). Conclusion: Combined prophylaxis with enalapril and carvedilol may prevent LVSD in patients with non-metastatic breast cancer treated with anthracyclines containing chemotherapy ± trastuzumab. The clinical relevance of this strategy should be confirmed in larger randomized studies. Key words: Cardioprotection, breast cancer, cardiotoxicity, Anthracyclin, trastuzumab</p>	<ol style="list-style-type: none"><li>1- Title changed</li><li>2- Corrections done and required fields added</li><li>3- Abbreviations are explained under each table and in the allocated part</li><li>4- Manuscript was revised again</li></ol>

## Review Form 1.6

	<p>It should be:</p> <p><b>Background:</b> 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.</p> <p><b>Objectives:</b> 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.</p> <p><b>Patients and Methods:</b> 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&lt;45%) or deterioration in LV diastolic function.</p> <p><b>Results:</b> 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, 16 patients were given 6 cycles ANTC and 18 patients received trastuzumab (as per the guidelines [issued by which society/institution?]) for adjuvant and neoadjuvant chemotherapy in early breast cancer).</p> <p>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: 0.048).</p> <p><b>Conclusion:</b> 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.</p> <p><b>Keywords:</b> Cardioprotection, breast cancer (BC), cardiotoxicity, anthracyclines, trastuzumab</p> <p>P # 3 Patients and Methods</p> <p>A table with patients' inclusion/exclusion criteria can be added.</p> <p>P # 10 Discussion</p> <p>Adding strengths and limitations would be helpful.</p> <p>P # 11 Conclusion</p> <p>It is:</p> <p>The concomitant use of ACEIs 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 outweigh the risks and benefits of cardiotoxic drugs in cancer patients. Identification of patients at risk for cardiotoxicity and is important but is still inadequate using the current methods e.g. LVEF and cardiac biomarkers.</p> <p>Suggested:</p> <p>The concomitant use of ACEIs 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</p>	
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Review Form 1.6

	<p>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).</p> <p>P # 11</p> <p>Adding the list of abbreviations at the end would be useful.</p> <p>Thank you</p>	
Minor REVISION comments	<p>The entire MS should be improved RE: grammar, clarity, and style.</p>	
Optional/General comments	<p>MS requires a revision</p>	

PART 2:

	Reviewer's comment	Author's comment (if agreed with reviewer, correct the manuscript and highlight that part in the manuscript. It is mandatory that authors should write his/her feedback here)
Are there ethical issues in this manuscript?	(If yes, Kindly please write down the ethical issues here in details)	