The Efficiency of Statins in the Protection of Anthracycline-Induced Cardiomyopathy. A Randomized Control Study from Egypt

Hadeya A[1,2], Ibrahim A[3], Abdeen M[4], Ahmed S[5]

[1] Oncology Department at University College London Hospital NHS Foundation Trust
[2] Clinical Oncology Department and Nuclear Medicine, Faculty of Medicine, New Valley University, Egypt
[3] Cardiology Department, Faculty of Medicine, Aswan University, Egypt
[4] Clinical Oncology Department Faculty of Medicine, Cairo University, Egypt
[5] Clinical Oncology Department and Nuclear Medicine, Faculty of Medicine, Suez University, Egypt

Abstract:

Background: Antineoplastic agents of the anthracycline (ANT) group are used in many forms of malignancies. They might lead to irreversible cardiomyopathy (CMP). Statins can reduce the risk of ANT-induced cardiotoxicity through their significant pleiotropic effects, antioxidative and anti-inflammatory properties.

Aim of work: To evaluate whether (Simvastatin in dose 40 mg) verses (low dose Simvastatin 10 mg +Ezetimibe 10 mg) could protect cardiotoxicity of ANT which could lead to ANT induced cardiomyopathy.

Methodology: Total 105 female breast cancer patients, mean age of 50.7+ 8 years who had ANT chemotherapy were enrolled. They were randomized into (Simvastatin in dose 40 mg) 30 patients, (low dose Simvastatin 10 mg + Ezetimibe 10 mg) 30 patients and ANT control group 45 patients. The study done between Jan 2018 to Jan 2020 in Clinical Oncology Department, Aswan University in Egypt. The therapy continued for 6 months. Evaluate the mean decline difference of the left ventricular ejection fraction (LVEF) at beginning of ANT chemotherapy then after ending of 4 cycles.

Results: The mean decline difference in Left ventricular ejection fraction (LVEF) was statistically significant among (Simvastatin40mg) group to Anthracycline control group P< 0.001 (6.67 ± 4.02% vs 9.22 ± 3.77). No statistically significant differences between (Simvastatin10mg with Ezetimibe 10 mg) group and ANT control group P= 0.08 (7.33 ± 4.12% vs 9.22 ± 3.77) or between Simvastatin group and Simvastatin with Ezetimibe group (6.67 ± 4.02 vs. 7.33 ± 4.12%; P= 0.08). The percentage of decline > 10% of the LVEF after 6 months in 3 studied groups was statistically significantly lower among both (Simvastatin 40mg group) and (Simvastatin10mg with Ezetimibe 10mg) group (20%) in comparison to ANT control group (46.7%), P= 0.01.

Conclusions: The statins do exert protective cardiovascular effects not solely from their lipid-lowering capacity but also from their anti-inflammatory effect. The dose of the statin plays a crucial rule in cardioprotective properties in ANT chemotherapy.

Key words: Statins, Anthracycline cardiomyopathy, dose, simvastatin, ezetimibe, cardiotoxicity

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Authors Information:

Ahmed Hadeya
Oncology Department at University College London Hospital NHS Foundation Trust, and Clinical Oncology Department and Nuclear Medicine, Faculty of Medicine, New Valley University, Egypt,
email: doc.ahmed.hadeya6236@gmail.com

Ayman Ibrahim
Cardiology Department, Faculty of Medicine, Aswan University, Egypt,
email:ayman.asham@yahoo.com

Mohamed Abdeen
Clinical Oncology Department Faculty of Medicine, Cairo University, Egypt
email:Mohamed_abdeen2002@yahoo.com

Soha Ahmed
Clinical Oncology Department and Nuclear Medicine, Faculty of Medicine, Suez University, Egypt
email:drsohaaa@gmail.com

Corresponding Author:
Ahmed Hadeya
Oncology Department at University College London Hospital NHS Foundation Trust, and Clinical Oncology Department and Nuclear Medicine, Faculty of Medicine, New Valley University, Egypt,
email: doc.ahmed.hadeya6236@gmail.com

Introduction:

The anthracycline anticancer drug is an effective and frequently used chemotherapeutic agent for various malignancies [1]. The successful use of anthracycline has been hampered by toxicities such as hematopoietic suppression, nausea, vomiting, extravasation, and alopecia, yet the most feared side-effect is cardiotoxicity [2].

Hydroxymethylglutaryl-CoA (HMG-CoA) reductase inhibitors, also known as "statins", which is first choice for the treatment of hypercholesterolemia since 1987 [3]. In addition to decrease cholesterol synthesis, they exhibit anti-inflammatory properties, reduce oxidative and nitrosative stress, inflammatory cytokines and reduce deleterious heart tissue remodelling [4].

In Acar et al 2011, patients under Anthracycline chemotherapy randomized to receive either atorvastatin 40mg for six months or control. This study showed that patient who had received atorvastatin 40mg preserved their mean left ventricular ejection fraction (LVEF) after six months of chemotherapy than control group which was statically significant [5].

Ezetimibe inhibits intestinal and biliary cholesterol absorption when used alone or in combination with statin therapy [6, 7]. Combination therapy trials using ezetimibe plus statin have shown greater efficacy in terms of low density lipoprotein cholesterol (LDL-C) reduction than monotherapy with ezetimibe or statin alone [8]. In our study, our aim is to evaluate whether low dose Simvastatin 10 mg plus Ezetimibe 10 mg versus Simvastatin in dose 40 mg could attenuate cardiotoxic effect of Anthracycline which could lead to Anthraycline induced cardiomyopathy.

Subject and Methods:

This randomized clinical study was conducted on 105 proven pathologically cancer patients candidate for Anthracycline at Clinical Oncology Department and Cardiology Department in Aswan University Hospital during the period from March 2018 to September 2019. Patients were randomized into the three study arms using a closed opaque envelope system to ensure allocation concealment. The study was conducted in a double-blind design, whereby neither the participants nor the investigators responsible for outcome evaluation were aware of group assignments, this approach minimized both selection and observer bias.

The study included female patients with age group > 18 years, who are candidate for Anthracycline chemotherapy and have no sensitivity regard simvastatin and Ezetimibe.

While patients who had a history of chemotherapy or radiotherapy, patients with symptoms of heart failure and or left ventricular (LV) dysfunction at baseline echocardiography < 50 % or patients with a history of any cardiac disease (congenital, valvular, ischemic, etc.) which could affect cardiac function, patients who receive any other medications which could affect cardiac function or already on statin therapy, having sensitivity to simvastatin and Ezetimibe or patients below 18 year were excluded from the study.

After fulfilling inclusion and exclusion criteria, patients were divided into three groups:

Arm A: Control group: Fourty five patients received Antracycline chemotherapy.

Arm B: Anthracycline chemotherapy plus Simvastatin dose (40 mg): Thirty patients received Anthracycline chemotherapy plus Simvastatin 40mg once daily at night with food, regardless of their baseline lipid values.

Arm C: Anthracycline Chemotherapy plus low dose Simvastatin and Ezetimibe (10mg/10mg): Thirty patients received Anthraycline chemotherapy plus Simvastatin 10mg and Ezitimibe 10mg once daily at night with food, regardless of their baseline lipid values.

Evaluation:

1- History:

All Patients underwent full history regard their medical history include previous liver, cardiac, renal disease before start Anthracycline chemotherapy.

2- Physical examination:

All patient underwent full physical examination before each cycle of Anthracycline chemotherapy for detection of jaundice and any musculoskeletal pain in form of muscle strength grading in grade from 0 to 5 in which.

- Grade 0: No muscle activation.
- Grade 1: Trace muscle activation, such as a twitch, without achieving full range of motion.
- Grade 2: Muscle activation with gravity eliminated, achieving full range of motion.
- Grade 3: Muscle activation against gravity, full range of motion.
- Grade 4: Muscle activation against some resistance, full range of motion.
- Grade 5: muscle activation against examiner's full resistance, full range of motion and assessment of pain by universal pain assessment tool uses the faces or behavior observation to interpret expressed pain even patient cannot communicate his/her intensity.

3 - Laboratory:

All patient underwent laboratory investigations before and after Anthracycline chemotherapy which include complete blood count (CBC), liver function, kidney function and C-reactive protein (CRP).

4 - Radiological:

All patients underwent Echocardiography before start Anthracycline chemotherapy and after 6 months to evaluate LVEF.

Echocardiographic examination was performed by using Philips IE 33© machine, X5-1 probe with simultaneous ECG tracing.

Ejection Fraction by 2D modified Simpson method [9] as follow:

- Apical 4-champers view (A4C) was acquired making sure that endocardial border was well visualized.
- Freeze the image and scroll backward and forward to identify the frame at end diastole (identifying a frame where the ventricle appears to have the largest volume; or with the ECG trace, where the peak of the R wave corresponds to end-diastole).
- Measurement menu was opened and LV volumes then (A4C diastole) were selected.
- The curser was placed on the endocardial border where the anterior mitral leaflet meets the interventricular septum and trace the entire endocardial border of the left ventricle. So the LV volume at diastole was calculated (LVEDV).

- The frozen image was then scrolled forward or backward to identify a frame at end-systole (this can be done by identifying a frame where the ventricle appears to have the smallest volume or correlating with the ECG trace, where the peak of the T wave corresponds to end-systole).
- A4C systole was selected from measurement menu then the outline endocardial borders of LV were traced so the LV volume at systole was calculated (LVESV).
- The machine calculated the EF automatically using this formula: EF = (LVEDV-LVESV)/LVEDV

Echocardiograms were analyzed by a cardiologist who was unaware of each patient's treatment protocol, cumulative doses of anthracyclines, and potential risk factors. The echocardiographic evaluation consisted of two-dimensional echocardiography and Doppler cardiography for the qualitative assessment of left ventricular regional wall motion. Left ventricular end-diastolic and end-systolic dimensions, fractional shortening (FS), or left and right systolic time interval indexes were measured by a single skilled observer in accordance with the recommendations of American Society of Echocardiography (9).

Follow up:

- During Anthracycline chemotherapy:

Clinically:

Full history and physical examination scheduled before each Anthracycine chemotherapy cycle every 3 weeks for 6 months for symptom of musculoskeletal pain, jaundice and change in color of urine.

Laboratory:

Complete blood picture (CBC), kidney function and liver function done before start each Anthracycline chemotherapy cycle and after 6 months.

- After the end of Anthracycline chemotherapy:

Clinically:

Full history and physical examination done after finish Anthracycine chemotherapy cycle for symptom of musculoskeletal pain, jaundice, color of urine.

Laboratory:

CBC, liver, kidney function and CRP done after finish Anthracycline chemotherapy.

Radiological:

Echocardiography done after finish Anthracycline chemotherapy to evaluate LVEF.

End Points

The primary end point was evaluating LVEF at beginning of Anthracyclie chemotherapy then after ending of Anthracycline chemotherapy cycles. The secondary end points were evaluating liver function tests before each cycle of Anthracycline chemotherapy and after the end of chemotherapy cycles, evaluating C-reactive protein (CRP) at the beginning and after ending of Anthracycline chemotherapy and evaluating musculoskeletal pain.

Statistical analysis:

Data were summarized using frequencies and mean ± standard deviation (SD). The left ventricular ejection fraction (LVEF) in each patient group was analyzed using ANOVA or paired t-tests, as appropriate. Differences between groups were assessed using Pearson's chi-square test or Fisher's exact test, while correlations were examined through Pearson correlation coefficients. A two-sided p-value < 0.05 was considered statistically significant. The study was powered at 80%, with the sample size calculated to detect a clinically relevant difference in LVEF before and after anthracycline chemotherapy, assuming a standard deviation of 8.25 and a significance level (α) of 0.05. ANOVA and paired t-tests were prespecified for group comparisons.

Results:

The mean age of arm A, B and C is 51.16 ± 8.49, 50.73 ± 8.54 and 50.13 ± 12.37 years, respectively with a majority of the percent premenoupasal females in the three arms 60%, 63.3% and 63.3%, respectively.

Right breast was the most frequent affected side in the three randomized arms. There were only two women had bilateral breast cancer treated in arm C. Positive family history of breast cancer was presented in five patients; three patients (6.7%) in arm A, one patient (3.3%) in arm B and one patient (3.3%) in arm C.

History of combined oral contraceptive was presented in 18 (40%), 12 (40%), and 8 (26.7%) patients of arm A, B and C, respectively. Diabetes mellitus and hypertension were presented in 7 (15.6%) and 9 (20%) patients of arm A, 2 (6.7%), and 4 (13.3%) patients of arm B and 5 (16.7%) and 2 (6.7%) patients of arm C, respectively. The patient's characteristic is shown in table 1.

Characteristics of tumor in randomized arms:

It was found in arm A that 2 (4.4%), 40 (88.9%), and 3 (6.7%) women had T1, T2 and T3 stage respectively. Regarding N stage in such group; 9 (20%), 15 (33.3%), 13 (28.9%), 8 (17.8%) patients had N0, N1, N2 an.d N3 stage respectively. Two patients had distant metastasis in arm A. Positive ER, positive PR and positive Her-2 were presented in 38 (84.4%), 38 (84.4%), and 2 (4.4%) patients, respectively while mean Ki 67 expression was 19.60 ± 8.52%. Lymphocytic infiltration, tumor emboli, and extracapsular invasion were found in 7 (15.6%), 9 (20%), and 1 (2.2%) patient, respectively in arm A (Figure 2,3).

In arm B, four (13.3%), 23 (76.7%), and 3 (10%) patients had T1, T2 and T3 stage respectively. N stage in such group; 8 (26.7%), 12 (40%), 7 (23.3%) and 3 (10%) patients had N0, N1, N2 and N3 stage respectively. Two patients had distant metastasis in arm B. Positive ER, positive PR and positive Her-2 were presented in 22 (73.3%), 24 (80%), and 1 (3.3%) patients, respectively while Mean Ki 67 expression was 22.46 ± 10.78%. Lymphocytic infiltration, tumor emboli, and extracapsular invasion were found in 5(16.7%), 8 (26.7%), and 3 (10%) patients, respectively of arm B.

In arm C; five (16.7%), 19 (63.3%), and 6 (20%) patients had T1, T2 and T3 stage respectively. N stage in such group; 7 (23.3%), 11 (36.7%), 11 (36.7%) and 1 (3.3%) patients had N0, N1, N2 and N3 stage respectively. Only one patient had distant metastasis in arm C. Positive ER, positive PR and positive Her-2were presented in 24 (80%), 25 (83.3%), and 1 (3.3%) patients, respectively while mean Ki 67 expression was 21.30 ± 9.65%. Only one patient had lymphocytic infiltration, and two patients had tumor emboli, and none of them had extracapsular invasion of arm C (Table 2).

Echocardiographic parameters in randomized arms:

The mean decline difference in Left ventricular ejection fraction (LVEF) was statistically significant lower among arm B (Simvastatin 40mg) to arm A (Anthracycline control group) (6.67 ± 4.02% vs. 9.22 ± 3.77%, P< 0.001). No statistically significant differences between arm C (Simvastatin 10mg with Ezetimibe 10mg) and arm A (ANT control group) (7.33 ± 4.12% vs. 9.22 ± 3.77%, P= 0.08) or between arm B and arm C (6.67 ± 4.02% vs. 7.33 ± 4.12%, P= 0.63) (Table 3) (Figure 4).

P value was significant if < 0.05. LVEF: left ventricular ejection fraction, LVEDD: left ventricular end diastolic diameter; LVESD: left ventricular end systolic diameter; P indicates significant difference between different groups. P1 compares between arm A and arm B. P2 compares between arm A and arm C. P3 compares between arm B and arm C

Percentage of decline difference above 10% of the LVEF after 6 months in 3 studied groups was statistically significantly lower among both arm B (Simvastatin 40mg group) and arm C (Simvastatin10mg with Ezetimibe 10mg) group (20%) in comparison to arm A (ANT control group) (46.7%), P= 0.01. (Figure 5) (Table 4).

In our data we measured the decline of LVEF below 55% in the three randomized arms after 6 months of chemotherapy and we concluded that it is not statistically significant (P=0.69). The LVEF was below 55% in 7 (15.6%) patients in arm A, 3 (10%) patients in arm B and 3 (10%) patients in arm C. (Figure 6) (Table 5).

One patient in arm A complained by dyspnea and palpitation after 6 months of therapy while all patients in randomized arms were asymptomatic.

Prechemotherapy and postchemotharpy laboratory data of randomized arms:

Prechemotherapy CRP was statistically significantly higher among arm B in comparison to arm A (12.64 ± 6.56 mg/dl vs.7.95 ± 6.56 mg/dl, P= 0.01).

Postchemotherapy CRP at six months was statistically significantly increased among arm A in compare to prechemotherapy CRP in the same arm (13 ±8.15 mg/dl vs. 7.95 ± 6.56 mg/dl, P= 0.01) (Figure 7) (Table 6). Postchemotherapy CRP at six months in arm B and C showed no significant difference with their precheomtherapy CRP.

In other labs, there was no statistically significant difference in the three randomized arms.

Prechemotherapy and postchemotherapy muscle pain in randomized arms:

It was noticed that all patients in the three randomized arms prechemotherapy and postchemotherapy had no change in musculoskeletal pain chart.

All patients had no pain prechemotherapy with exception of one patient from arm A and arm C had mild pain. Pain scale postchemotherapy was zero with exception of five patients had mild pain and four patients had moderate pain. All randomized arms had insignificant differences as regarding pain scale, and waist circumference and body mass index.

Correlation between percentage of decline in LVEF and lipid profile:

Correlations between percentage of decline in LVEF and lipid profile showed in Table 7, 8. The percentage of decline in LVEF either above 10% or below 10% in arm B and C had insignificant correlation with their prechemotherapy lipid profile either normal or high.

Correlation between percentage of decline in LVEF and percentage of increase in CRP:

Correlations between percentage of decline in LVEF and increase in CRP in table 9. It was noticed that percentage of decline in LVEF in all randomized arms had insignificant correlation with increase in CRP.

Correlation between percentage of decline in LVEF and doses of Anthracycline:

Correlations between percentage of decline in LVEF and doses of Anthracycline in table 10. It was noticed that percentage of decline in LVEF in all randomized arms had insignificant correlation with cumulative doses of Anthracycline. Mean dose of Anthracycline was 430.5 ± 41.7 mg/m^2, 438.8 ± 41.4 mg/m^2 and 424.7 ± 55.1 mg/m^2 in arm A, B and C, respectively.

Correlation between percentage of decline in LVEF and age:

Correlations between percentage of decline in LVEF and age of patients show in table 11. It was noticed that percentage of decline in LVEF in all randomized arms had insignificant correlation with age of patients.

Risk factors in each studied group based on postchemotherapy LVEF:

Risk factors in each studied groups based on postchemotherapy LVEF in table 12. It was noticed that patients with postchemotherapy LVEF above 55% and those with postchemotherapy LVEF below 55% in all randomized arms had insignificant differences as regarding diabetes mellitus and hypertension.

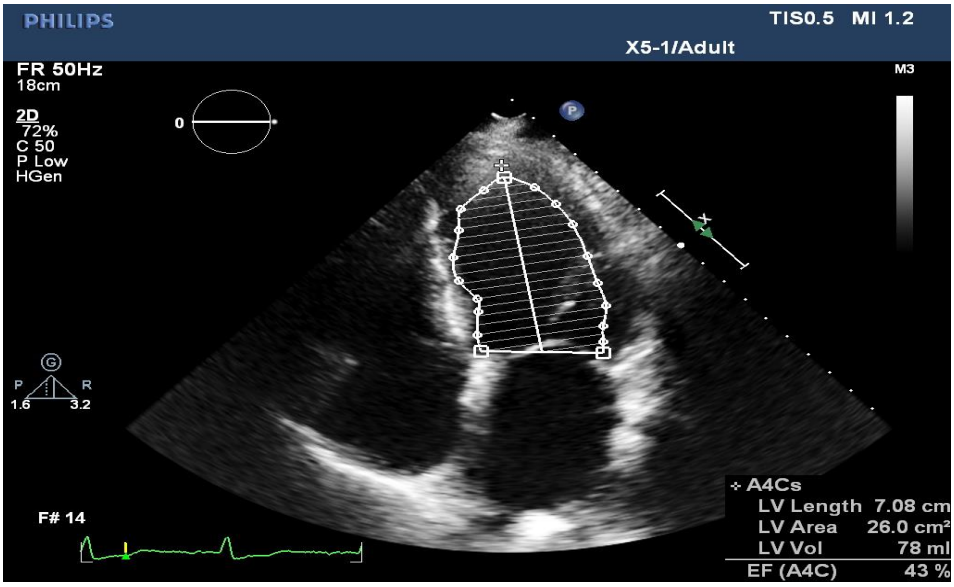

Figure 1. Measurement of EF by 2D Simpson method by Philips IE33 machine

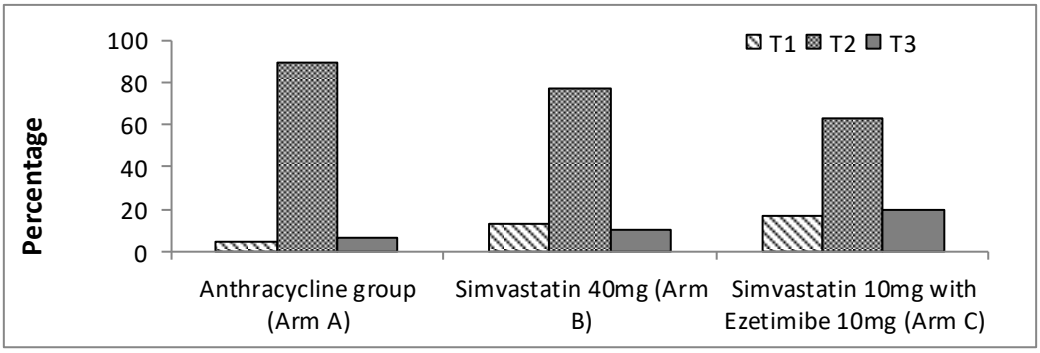

Figure 2. T stage in studied groups

Figure 3. Tumor emboli in studied groups

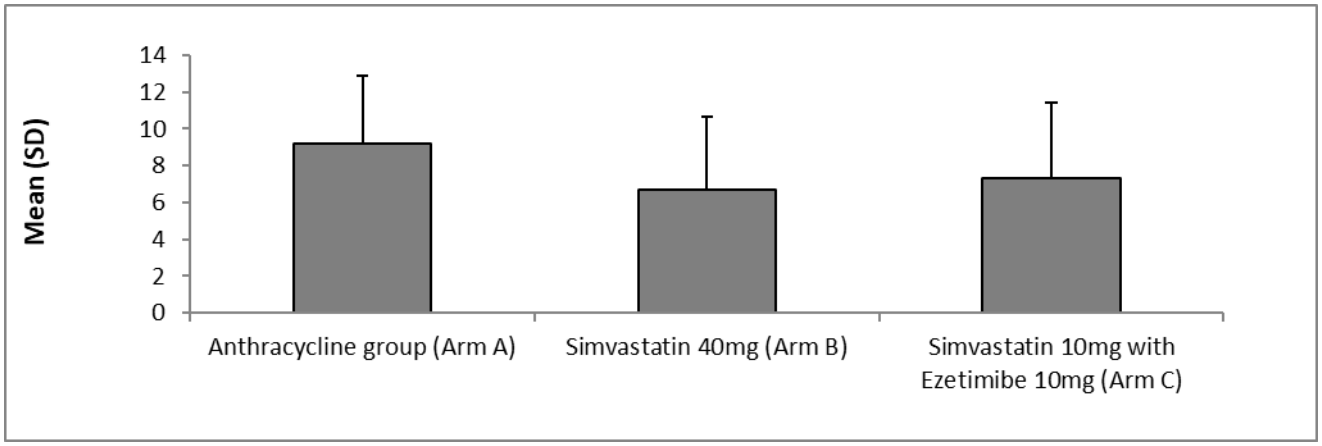

Figure 4. Mean decline difference of LVEF between prechemotherapy and 6 months of chemotherapy in the randomized arms, LVEF: left ventricular ejection fraction

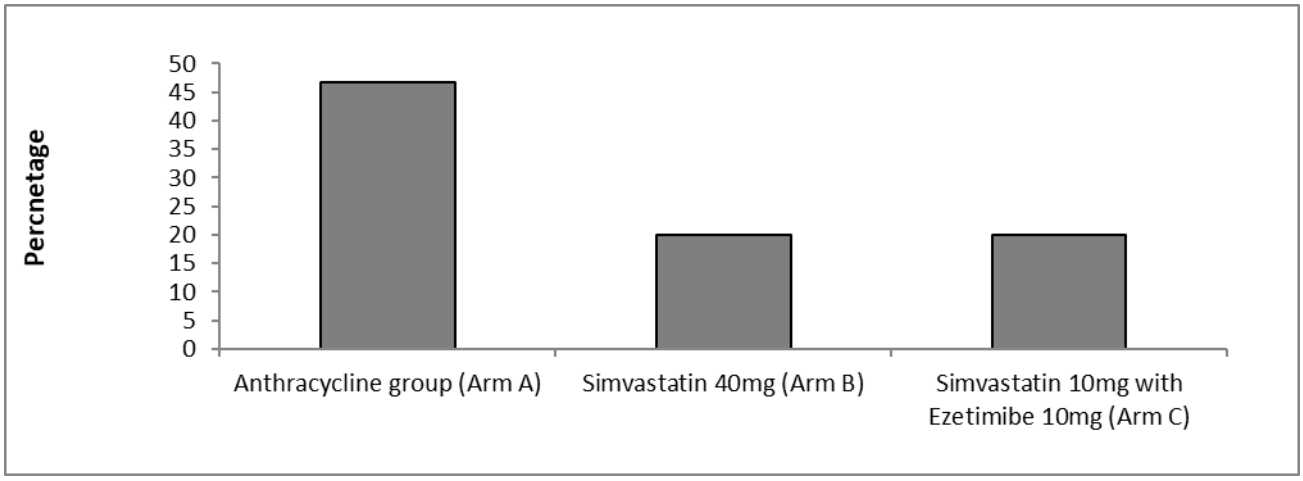

Figure 5. Percentage of decline difference above 10% of the LVEF after 6 months.

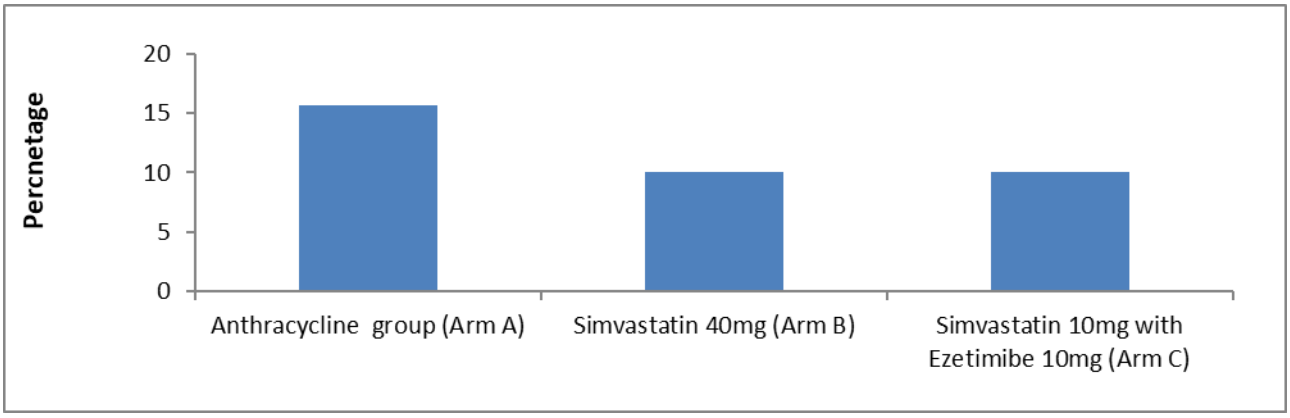

Figure 6. 6-month ejection fraction < 55% in patients after six months of therapy.

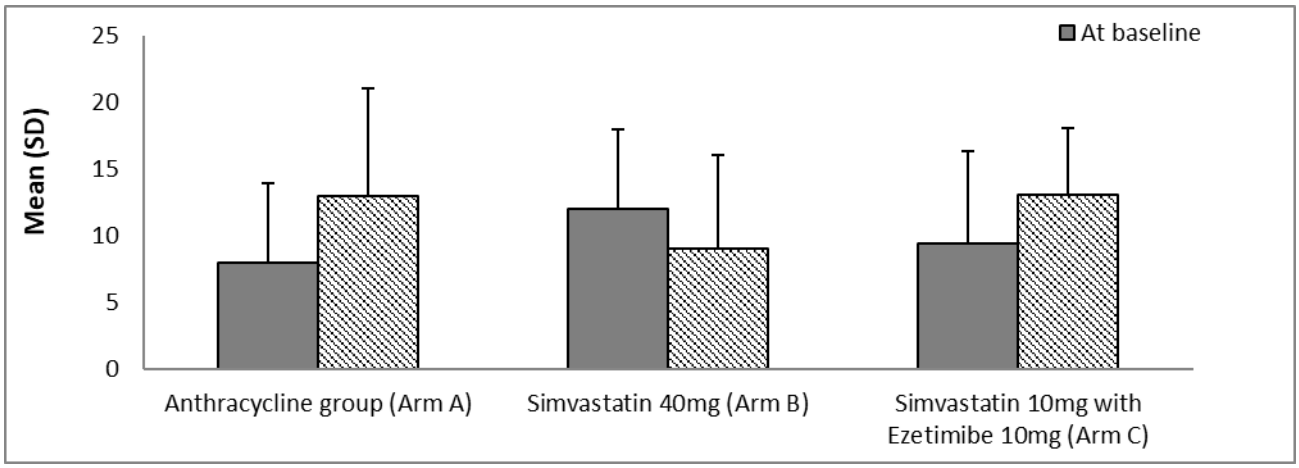

Figure 7. Prechemotherapy and postchemotherapy C-reactive proteins in randomized arms.

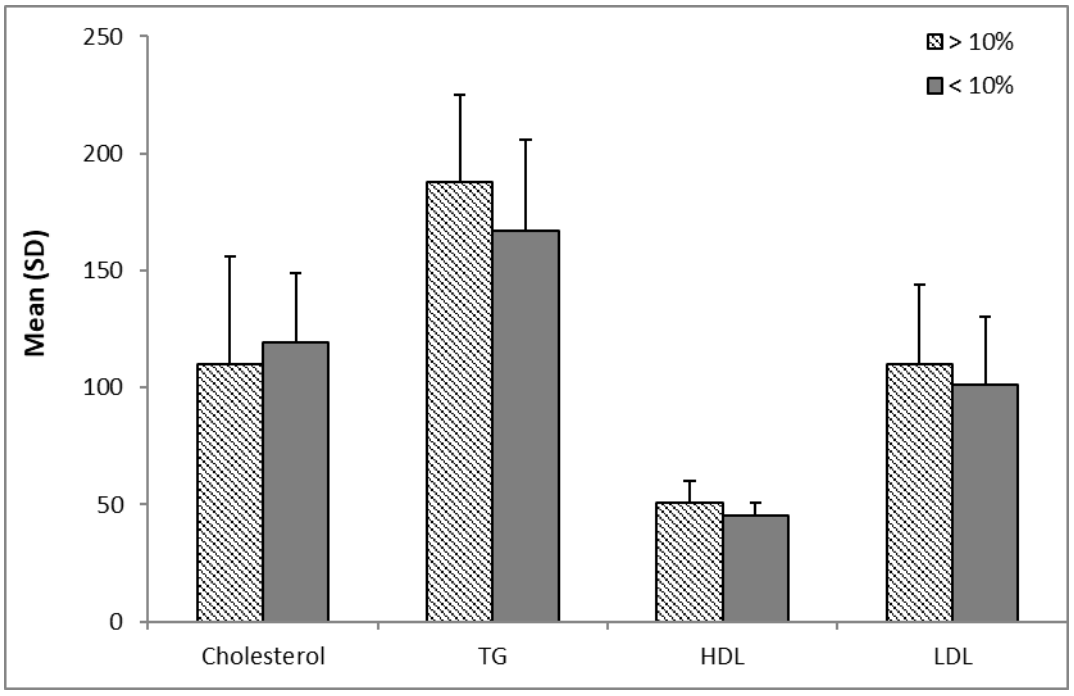

Figure 8. Correlation between lipid profile and percentage of decline in LVEF in Arm B “Simvastatin 40mg group”

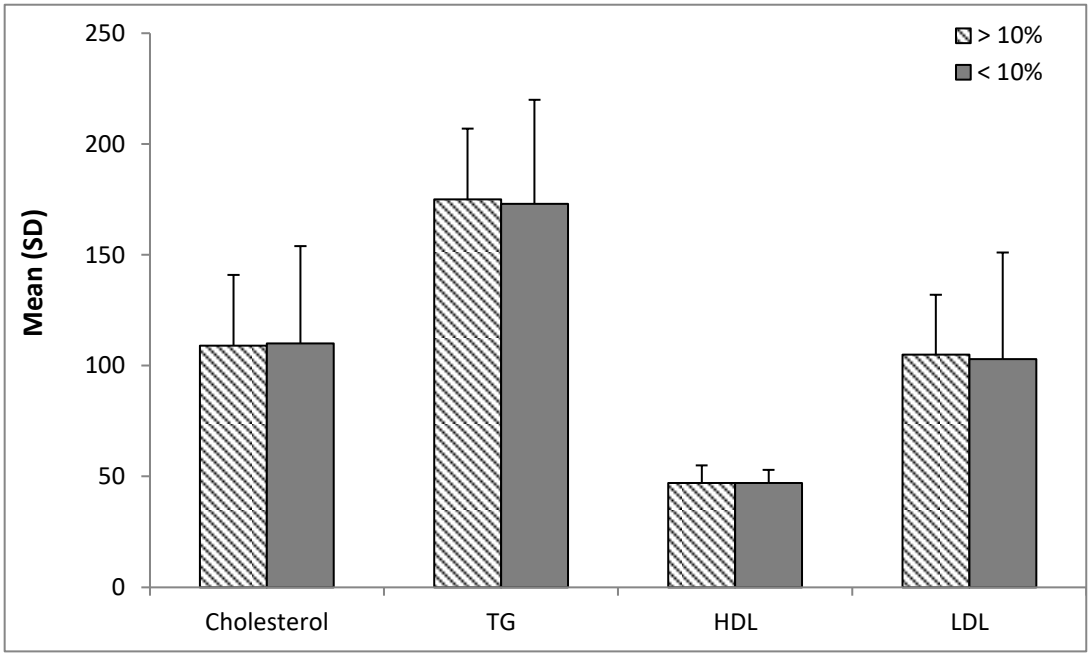

Figure 9. Correlation between lipid profile and percentage of decline in LVEF in Arm C "Simvastatin 10mg with Ezetimibe 10mg group"

Table 1. Demographic data in randomized arms

	The whole study (n=105)	Anthracycline group Arm A (n= 45)	Simvastatin Arm B (n= 30)	Simvastatin with Ezetimibe Arm C (n= 30)	P
Age, y					
Median age (IQR)	50	50	50	48	
Mean age (SD) ± range	50.74 ± 9.74	51.16 ± 8.49	50.73 ± 8.54	50.13 ± 12.37	0.834
Menopausal status					
Premenopausal (%)	65 (61.9%)	27 (60%)	19 (63.3%)	19 (63.3%)	0.453
Postmenopausal (%)	40 (38.1%)	18 (40%)	11 (36.7%)	11 (36.7%)	
Affected side					
Right (%)	60 (57.1%)	23 (51.1%)	17 (56.7%)	20 (66.7%)	0.103
Left (%)	43 (40.9%)	22 (48.9%)	13 (43.3%)	8 (26.7%)	
Bilateral (%)	2 (1.9%)	0	0	2 (6.7%)	
Positive family history of breast cancer (%)	5 (4.7%)	3 (6.7%)	1 (3.3%)	1 (3.3%)	0.732
History of COCs (%)	38 (36.2%)	18 (40%)	12 (40%)	8 (26.7%)	0.438
Diabetes mellitus (%)	14 (13.3%)	7 (15.6%)	2 (6.7%)	5 (16.7%)	0.219
Hypertension (%)	15 (14.2%)	9 (20%)	4 (13.3%)	2 (6.7%)	0.335
Body mass index (SD)	33.3 ± 14.2	33.2 ± 13.9	34.26 ± 12.94	32.46 ± 14.1	0

P value was significant if < 0.05. COCs: combined oral contraception.

Table 2. Characteristics of tumor in randomized arms.

	Anthracycline group Arm A (n= 45)	Simvastatin Arm B (n= 30)	Simvastatin with Ezetimibe Arm C (n= 30)	P
TMN staging				
T stage				
T1 (%)	2 (4.4%)	4 (13.3%)	5 (16.7%)	0.563
T2 (%)	40 (88.9%)	23 (76.7%)	19 (63.3%)	
T3 (%)	3 (6.7%)	3 (10%)	6 (20%)	
N stage				
N0 (%)	9 (20%)	8 (26.7%)	7 (23.3%)	
N1 (%)	15 (33.3%)	12 (40%)	11 (36.7%)	0.825
N2 (%)	13 (28.9%)	7 (23.3%)	11 (36.7%)	
N3 (%)	8 (17.8%)	3 (10%)	1 (3.3%)	
Distant metastasis (%)	2 (4.4%)	2 (4.4%)	1 (3.3%)	0.67
Biological Characteristics				
Positive PR (%)	38 (84.4%)	24 (80%)	25 (83.3%)	0.879
Positive Her-2 (%)	2 (4.4%)	1 (3.3%)	1 (3.3%)	0.958
Mean Ki 67 ± SD	19.60 ± 8.52	22.46±10.78	21.30 ± 9.65	0.204
Pathological characteristics				
Lymphocytic infiltration (%)	7 (15.6%)	5 (16.7%)	1 (3.3%)	0.203
Tumor emboli (%)	9 (20%)	8 (26.7%)	2 (6.7%)	0.120
Extracapsular invasion (%)	1 (2.2%)	3 (10%)	0	0.170

P value was significant if < 0.05. ER: estrogen receptor; PR: progesterone receptor

Table 3. Echocardiographic findings in randomized arms

	Anthracyclin group Arm A (n= 45)	Simvastatin Arm B (n= 30)	Simvastatin with Ezetimibe Arm C (n= 30)	P	P1	P2	P3
Mean LVEF (%) ±SD Mean LVEF prechemotherapy	68.46 ± 4.94	67.70 ± 6.01	69.40 ± 6.53	0.51	0.57	0.49	0.25
Mean LVEF 6 months after chemotherapy	59.24 ± 5.24	61.46 ± 6.31	62.06 ± 5.94	0.08	0.10	0.40	0.68
Mean decline difference of LVEF between prechemotherapy and 6 months of chemotherapy	9.22 ± 3.77	6.67 ± 4.02	7.33 ± 4.12	0.01	<0.001	0.08	0.63

Table 4. Percentage of decline difference above 10% in LVEF after 6 months in randomized arms

	Anthracycline control group Arm A (n= 45)	Simvastatin Arm B (n= 30)	Simvastatin with Ezetimibe Arm C (n= 30)	P
Percentage of decline difference above 10% of the LVEF after 6 months	21 (46.7%)	6 (20%)	6 (20%)	0.01

P value was significant if < 0.05. LVEF: left ventricular ejection fraction

Table 5. 6-month Ejection Fraction below 55% in randomized arms

	Anthracycline group Arm A (n= 45)	Simvastatin Arm B (n= 30)	Simvastatin with Ezetimibe Arm C (n= 30)	P
6-month LVEF below 55%	7 (15.6%)	3 (10%)	3 (10%)	0.69

P value was significant if < 0.05. LVEF: left ventricular ejection fraction. P indicates significant difference between different groups.

Table 6. prechemotherapy and postchemotherapy C-reactive protein of studied groups

	Anthracyclin group Arm A (n= 45)	Simvastatin Arm B (n= 30)	Simvastatin with Ezetimibe Arm C (n= 30)	P
C-reactive proteins (mg/dl)				
prechemotherapy	7.95 ± 6.56	12.64 ± 6.56	9.37 ± 7.12	0.01
6 months				
postchemotherapy	13 ± 8.15	9.37 ± 7.12	13.13 ± 5.26	0.80

P value was significant if < 0.05. P indicates significant difference between different groups.

Table 7. Correlation between lipid profile and percentage of decline in LVEF in Arm B "Simvastatin 40mg group"

	Percentage of decline in LVEF		
	Above 10%	Below 10%	P value
Triglyceride level	110.33 ± 37.16	119.46 ± 48.60	0.67
Triglyceride class			0.70
Normal	5 (83.3%)	20 (83.3%)	
High	1 (16.7%)	4 (16.7%)	
Cholesterol level	184.50 ± 44.57	167.47 ± 37.94	0.34
Cholesterol class			0.12
Normal	3 (50%)	20 (83.3%)	
High	3 (50%)	4 (16.7%)	
High density lipoprotein level	51.66 ± 7.78	45.75 ± 9.11	0.15
High density lipoprotein class			0.50
Normal	5 (83.3%)	22 (91.7%)	
High	1 (16.7%)	2 (8.3%)	
Low density lipoprotein level	110.50 ± 44.23	101.87 ± 35.56	0.45
Low density lipoprotein class			0.34
Normal	4 (66.7%)	20 (83.3%)	
High	2 (33.3%)	4 (16.7%)	

P value was significant if < 0.05. LVEF: left ventricular ejection fraction; HDL: high density lipoprotein; LDL: low density lipoprotein

Table 8. Correlation between lipid profile and percentage of decline in LVEF in Arm C "Simvastatin 10mg with Ezetimibe 10mg"

	Percentage of decline in LVEF		
	Above 10%	Below 10%	P value
Triglyceride level	109.50 ± 38.90	110.58 ± 33.82	0.94
Triglyceride class			0.65
Normal	5 (83.3%)	19 (79.2%)	
High	1 (16.7%)	5 (20.8%)	
Cholesterol level	175.50 ± 48.78	173.79 ± 32.29	0.91
Cholesterol class			0.48
Normal	5 (83.3%)	17 (70.8%)	
High	1 (16.7%)	7 (29.2%)	
High density lipoprotein level	47.66 ± 4.92	47.58 ± 9.08	0.98
High density lipoprotein class			0.63
Normal	6 (100%)	22 (91.7%)	
High	0	2 (8.3%)	
Low density lipoprotein level	105.66 ± 43.25	103.79 ± 27.63	0.89
Low density lipoprotein class			0.65
Normal	5 (83.3%)	19 (79.2%)	
High	1 (16.7%)	5 (20.8%)	

P value was significant if < 0.05. EF: ejection fraction HDL: high density lipoprotein; LDL: low density lipoprotein

Table 9. Correlation between percentage of decline in LVEF and increase in CRP

	Percentage of decline in LVEF Anthracycline group Arm A		Simvastatin 40mg Arm B		Simvastatin 10mg with Ezetimibe 10mg Arm C	
	r	P	r	P	r	P
Increase in CRP	0.06	0.67	0.35	0.05	-0.26	0.16

P value was significant if < 0.05. LVEF: left ventricular ejection fraction; CRP: C-reactive protein

Table 10. Correlation between percentage of decline in LVEF and dose of Anthracycline

	Percentage of decline in LVEF Anthracycline group Arm A		Simvastatin 40mg Arm B		Simvastatin 10mg with Ezetimibe 10mg Arm C	
	r	P	r	P	r	P
Doses of Anthracycline	0.13	0.39	0.04	0.81	-0.22	0.24

P (significance of correlation). P value was significant if < 0.05. LVEF: left ventricular ejection fraction;

Table 11. Correlation between percentage of decline in LVEF and age of patients

	Percentage of decline in LVEF					
	Anthracyclin group Arm A		Simvastatin 40mg Arm B		Simvastatin 10mg with Ezetimibe 10mg Arm C	
	r	P	r	P	r	P
Age	0.18	0.25	0.30	0.10	0.31	0.08

P (significance of correlation). P value was significant if < 0.05. LVEF: left ventricular ejection fraction

Table 12. Risk factors based on postchemotherapy LVEF

	Postchemotherapy LVEF		
	≥ 55%	< 55%	P value
Arm A (Anthracycline group)			
Diabetes mellitus	6 (15.8%)	1 (14.3%)	0.70
Hypertension	7 (18.4%)	2 (28.6%)	0.43
Arm B (Simvastatin 40mg group)			
Diabetes mellitus	1 (3.7%)	1 (33.3%)	0.19
Hypertension	3 (11.1%)	1 (33.3%)	0.36
Arm C (Simvastatin 10mg with Ezetimibe 10mg group)			
Diabetes mellitus	4 (14.8%)	1 (33.3%)	0.43
Hypertension	2 (7.4%)	0	0.80

P value was significant if < 0.05.

Discussion:

Antineoplastic agents of the anthracycline (ANT) group are used in many forms of malignancies. they might lead to irreversible cardiomyopathy (CMP) through Cytotoxic free radicals resulted from interaction of anthracycline with the enzyme topoisomerase IIa, production of double strand DNA breaks promote oxidative and nitrosative stress in cardiomyocytes [10].

Statins commonly used to treat hypercholesterolemia. Also, they can reduce the risk of ANT-induced cardiotoxicity through their significant pleiotropic effects, antioxidative and anti-inflammatory properties [11].

The present study aimed to highlight the role of statin in cardioprotection. The mean decline difference in Left ventricular ejection fraction (LVEF) in the present study was statistically significant lower among arm B (Simvastatin 40mg) in comparison to arm A (Anthracycline control group (6.67 ± 4.02% vs 9.22 ± 3.77%, P< 0.001).

A similar pattern of results was obtained in Calvillo et al study. Forty-three patients received statins during anthracycline based chemotherapy with a median cardiac follow-up duration of 11 months, the adjusted final LVEF was lower in the control group than statin group. A significant change in LVEF was observed in the control group but not in the statin group. Upon adjusted analysis, statin treatment was independently associated with a lower risk of cardiotoxicity [12]. Noted in Chotenimitkhun et al study founded that measurement of LVEF in patients receiving anthracyclines with statins demonstrated no significant decrease in LVEF (P =0.14), whereas those not prescribed statins demonstrated a decrease in LVEF 6 months after recipient of anthracycline based chemotherapy [13].

Similar observations was reported by Acar et al study [14] which demonstrate no difference was observed in the mean EF of the statin group (61.3 ± 7.9% vs. 62.6 ± 9.3%, p = 0.144). However, the decrease in the control group was significant (62.9 ± 7.0% vs. 55.0 ± 9.5%, p < 0.0001). Therefore, mean reduction in LVEF were significantly lower in the statin arm as compared with the control group p < 0.0001.

In the present study, there was nearby statistically significant differences in mean decline difference in LVEF between arm C and arm A (7.33 ± 4.12% vs 9.22 ± 3.77%, P= 0.08) also not statistically significant between arm B and arm C (6.67 ± 4.02 vs. 7.33 ± 4.12%, P= 0.63). To the best of our knowledge, this is the first study to compare Simvastatin in dose 40mg

with Simvastatin 10mg plus Ezetimibe 10mg regarding the context of cardioprotection in case of ANT chemotherapy admission. We observed that statins do exert protective cardiovascular effects and the standard dose of the statin admission (40mg) plays a crucial rule in cardioprotective properties in ANT chemotherapy. This was not the case Simvastatin 10mg plus Ezetimibe 10mg, we supposed those result due to anti-inflammatory effect of high dose statin.

In the present study, there was no statistically significant regarding decline of LVEF below 55% after 6 months of therapy (P=0.69), we reported that 7 patients (15.6%) in group A, 3 patients (10%) in group B and 3 patients (10%) in group C were observed with a LVEF below 55%. Similar observation was reported by Acar et al study where 1 patient in the statin group was observed with an EF below 50%, 5 patients in the control group were observed with values below 50% (p = 0.18) [14].

In our study, we observe that only one patient in group A complained by dyspnea and palpitation after 6 months of therapy. This observation explained in study by Cardinale et al, in which anthracycline chemotherapy–induced cardiotoxicity represents a that begins with subclinical myocardial cell injury, followed by an early asymptomatic LVEF reduction, and then progresses to symptomatic cardiac failure if untreated [15].

In our study, postchemotherapy C-reactive protein (CRP) at six months was statistically significantly increased among arm A in compare to prechemotherapy CRP in the same arm (13 ± 8.15 mg/dl vs. 7.95 ± 6.56 mg/dl, P = 0.01). Similar observation was reported by Acar et al study where there was a significant increase CRP in the control group (3.84 ± 0.89 mg/dl vs. 5.43 ± 1.78 mg/dl, p < 0.0001) [14].

Also in our study, there was no statistically significant difference between prechemotherapy CRP and postchemotherapy CRP at six months in arm B and C which was similar with Acar et al study where no significant change was observed in CRP after chemotherapy in the statin group [14].

In the present study, there was no change in musculoskeletal pain chart in all arms which was consistent with Robinson et al study where there was no occurrence of muscle pain in all groups [16].

Regarding CRP correlation with LVEF, we found a non-significant correlation between percentage of decline in LVEF and increase in CRP. A similar observation obtained by Correia et al. which demonstrate that CRP has no correlation with EF or angiographic finding but correlate with major cardiac event [17]. Therefore, CRP could not be a surrogate marker for monitoring the decline in LVEF that reflected on ANT chemotherapy induce cardiomyopathy.

Concerning about cumulative dose anthracycline, our study found that there was no correlation between percentage of decline in ejection fraction and doses of Anthracycline as mean dose of Anthracycline was (430.5 ± 41.7 mg/m^2, P =0.39), (438.8 ± 41.4 mg/m^2, P = 0.81) and (424.7 ± 55.1 mg/m^2, P = 0.24) in arm A, B and C respectively.

A similar pattern of correlation with doses of Anthracycline results was obtained in Drafts et al study that the magnitude of subclinical deterioration in cardiac and vascular function (change in LVEF%) is not correlated with the total amount of anthracycline received after treatment for cancer [18]. Zamorano et al study demonstrated that those treated for breast cancer malignancy experienced decreases in left ventricular performance. It is noteworthy that there was no correlation between the decrease in LVEF and the cumulative dose of doxorubicin-equivalent chemotherapy administered to participants in the study [19].

Additionally, percentage of decline in ejection fraction had a non-significant correlation with age of patients. A similar observation obtained by other study which demonstrate that change in LVEF had non-significant correlation with age of patients [20].

Our study also found that no significant correlation in patients with postchemotherapy LVEF after 6 months of therapy either > 55% or < 55% in all studied groups with diabetes mellitus and hypertension. Chotenimitkhun et al demonstrated that individuals receiving statins were older and often had diabetes mellitus (DM), hypertension (HTN), and hyperlipidemia (HLD) [13]. For those receiving statins, LVEF was 56.6% ± 1.4% at prechemotherapy and 54.1% ± 1.3% after 6 months from initiating anthracycline treatment (P = 0.15) A similar pattern of results was obtained in Khouri et al study which founded that cross-sectional study of 57 patients who were treated with standard-dose doxorubicin chemotherapy 28% of patients had hypertension, 21% were obese, 11% had hyperlipidemia and 12% had diabetes [21].

Conclusion:

Anthracyline chemotherapy is an important chemotherapy in treatment of many cancer. Despite of, it is crardiotoxicity which can be protected by using an alternative analogues to anthracycline, consideration to cumulative dose and use of cardioprotective drugs as statin.

The statins do exert protective cardiovascular effects not solely from their lipid-lowering capacity but also from their anti-inflammatory effect.

The dose of the statin plays a crucial rule in cardioprotective properties in ANT chemotherapy. Therefore, Simvastatin 40mg and its concomitant use with Anthracycline was associated with lower magnitude of reduction in LVEF and safe of liver toxicity.

Simvastatin 10mg plus ezetimibe 10mg might play role in cardioprotective properties in ANT chemotherapy but need more investigations.

Simvastatin 40mg and simvastatin 10mg plus ezetimibe 10mg have tolerable toxicity profile “liver function, muscle pain and CRP” in all treated patients with ANT chemotherapy.

List of abbreviations

- Antineoplastic agents of the anthracycline (ANT)
- Cardiomyopathy (CMP)
- Left ventricular ejection fraction (LVEF)
- low density lipoprotein cholesterol (LDL-C)
- C-reactive protein (CRP)
- Complete blood picture (CBC)
- fractional shortening (FS)
- anthracycline (ANT)

Authors' contributions

Dr. Mohamed Abdeen supervised the study and served as the principal investigator. Dr. Soha Ahmed contributed to the trial design and provided ongoing supervision and follow-up. Dr. Ayman Ibrahim performed and interpreted the echocardiographic assessments and provided cardiology follow-up. Ahmed Hadeya conducted the study, collected the data, and drafted the manuscript. All authors reviewed and approved the final manuscript.

Declarations

Ethical Approval and Consent to Participate

The study was reviewed and approved by the Institutional Review Board of Aswan University (IRB no. Asw. Uni./236/4/18). All procedures were carried out in line with relevant ethical guidelines and regulations. Informed consent was obtained from all participants before their involvement in the study.

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Competing Interests

The authors declare that they have no competing financial interests or personal relationships that could have influenced the work reported in this manuscript.

Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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