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ECHOCARDIOGRAPHIC CHANGES IN LEFT-VENTRICULAR DIMENSIONS AND LEFT-VENTRICULAR MASS IN BREAST CANCER PATIENTS SCHEDULED TO RECEIVE ANTHRACYCLINES

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Abstract

Anthracyclines (AT) are the cornerstone of adjuvant chemotherapy in breast cancer (BC) patients. Certain demographic parameters and risk factors predispose to anthracycline-induced cardiotoxicity (ATIC). Close echocardiography monitoring is crucial in diagnosing early cardiac changes, thus preventing further adverse cardiac events and withholding the cancer therapy.

This study aims to assess possible changes in left ventricular (LV) dimensions, wall thicknesses and LV mass according to certain demographic characteristics and cardiovascular (CV) risk factors, as well as their relations in patients with BC receiving ATs.

We present 30 patients with BC receiving ATs. Demographic parameters and risk factors are: age, body mass index, obesity, hypertension, diabetes, physical activity, risk for AT cardiotoxicity and total AT dose. The echocardiographic parameters followed are LV end-diastolic (LVDd) and end-systolic dimension (LVDs), wall thickness; interventricular septum (IVSd) and posterior wall (PW), as well as LV mass (LVM) and relative wall thickness. Statistical analysis included SPSS v.25.0

LV end-diastolic dimension (LVEDd) significantly increased at the control evaluation (p=0,026). Correlation between the differences in LVEDd and LVEDs between the two visits showed significant relation of the increase with higher indexed AT dose (p=0,007, p=0,030). Higher indexed AT dose was independent predictor for increased both LVEDd and LVEDs at the control evaluation.

AT provoke significant echocardiography changes in BC patients and frequent surveillance provides assessment of early changes as an introduction to CTRCD. Further investigation is needed for a more sensitive ATIC discussion.

Keywords: anthracyclines, breast cancer, echocardiography, left ventricular dimensions, left ventricular mass

Introduction

Breast cancer (BC) is the most common malignant disease in women and second leading cause of cancer death in United States in that population. In 2023, a new 297,790 women are expected to be diagnosed with invasive BC, and unfortunately 43,700 deaths are expected for the same year with overall 0,5% increased incidence rates per year [1].

Since the year 2000, the incidence of BC has been in constant decline, with as much as 7% in the US from 2002-2003[3]. BC death rates and overall mortality are also decreasing in these past 30 years, believed to be the result of earlier diagnosis and more therapeutic options. Along the swift development of the pharmaceutical oncology industry, the expansion of BC genetic and molecular diagnosis, the introduction of new and targeted chemotherapeutics (HT) and the raising field of cardio-oncology, the overall rates of induced remissions are increasing and the prognosis is good and promising [4].

More than half of newly diagnosed patients with BC will start some of the anthracycline (AT) protocols as the first therapeutic option in their treatment [5]. At the same time, ATs are probably the most reported HT group according to the possible side effects that negatively affect the overall outcome [6].

AT-induced cardiotoxicity (ATIC) is the most serious complication, and cancer therapy-related cardiac dysfunction (CTRCD) has been progressively recognized.

ATIC is progressive phenomenon of heart damage caused by generation of reactive oxygen radicals, resulting in DNA damage, cellular dysfunction and myocyte death. Despite the studies suggesting

that it is irreversible phenomenon, there is increasing evidence of myocardial recovery after AT-induced toxicity [2]. Strategies favoring early detection of subclinical cardiac dysfunction and close monitoring, especially in high-risk patients, reduce the severity of possible complications and significant left-ventricular (LV) dysfunction [7].

Pre-treatment cardiovascular (CV) toxicity risk assessment should be performed in every patient scheduled to receive ATs and risk stratification incorporates multiple risk factors to determine patient specific risk. Baseline risk stratification of patients with clinically significant level of possible ATIC, demands comprehensive prevention strategies and close collaboration in trained cardio-oncology team. Reviewing traditional CV risk factors, control of modifiable and lifestyle ones, evidence of prior or active cardiovascular disease (CVD) select a potential high-risk patient group, that needs complex clinical evaluation and serious therapy decisions [9].

Transthoracic echocardiography (TTE) is standard method for establishing previous history of CVD, as main risk factor predisposing to possible cancer therapy cardiotoxicity.

Further echocardiography surveillance during and after the cancer therapy is crucial for obtaining any cardiac changes significant to prelude CTRCD. On the other hand, demographic characteristics and patient's lifestyle habits present conflicting findings of mutual association with cardiotoxicity, so the need for larger studies is mandatory. Presence of diabetes mellitus (DM) [29], hypertension (HTA) [30], obesity [24], excessive alcoholic consumption [29], sedentary lifestyle [31] are all listed as risk factors for ATIC in BC patients. Recognizing overall patient's risk can safely guide further clinical examination, investigations and advanced preventive strategies, optimizing the opportunity to have best cancer treatment, without withholding possible cardiotoxic cancer therapy [10].

Aims

The aim of this study is to determine possible changes in LV dimensions, wall thicknesses and LV mass according to certain demographic characteristics and CV risk factors, as well as their relation in patients with BC receiving AT therapy.

Materials and methods

This was a clinical, prospective, multidisciplinary study including 30 patients with newly diagnosed BC scheduled to receive AT-containing HT protocol through University clinic for radiotherapy and oncology and followed by 2D TTE in the echocardiographic laboratory of the City General Hospital "8th September" in Skopje, in the period 2022-2023. The pre-set inclusion and exclusion criteria specified patients over 18 years, LV ejection fraction (LVEF%) >40%, absence of significant valvular disease, atrial fibrillation, hemodynamically unstable cardiac conditions or significant wall motion abnormalities and patients with poor image quality or estimated survival <6 months. Patients were subjected for basic risk stratification for ATIC according to the latest recommendations of the European Society of Cardiology (ESC) [9]. A baseline 2D TTE was performed on commercially available equipment (Vivid 7, GE, USA) with standard assessments of LV dimensions in accordance with the relevant association recommendations (11). Patients were assessed following recommended protocol according their overall cardiotoxic risk, including two visits, baseline and after 4th AT cycle in patients with mild and moderate risk, and additional visit after 2nd cycle in patients with high AT risk [6].

Assesment of certain demographic parameters and risk factors were obtained: age, body mass index (BMI), obesity, HTA, DM, practising of physical activity, AT cardiotoxicity risk level and total AT dose. The echocardiographic parameters that were monitored included LV chamber dimensions and wall thickness measurements, LV mass and relative wall thickness.

The participation in the research was voluntary, with already confirmed informed consent by the participants, and approved by the Ethics Committee at the Faculty of Medicine in Skopje.

Statistical analyses

Categorical parameters were summarized as percentages and continuous parameters as a mean standard +/- deviation. Comparison between groups was performed with the nonparametric Wilcoxon Sign Rank test for related pairs (same variable at first vs. second visit). Correlation between parameters was examined by Pearson and/or Spearman correlation. Multiple stepwise linear regression analysis was performed to determine independent predictors. All data analyses were performed using the statistical program SPSS version 25.0 (IBM SPSS, Inc, Chicago, Illinois). For all tests a value of $p<0.05$ was considered to be statistically significant.

Results

A total of 30 patients with newly diagnosed BC were treated in the study, with an average age of 52.5 ± 10.9. 96,7% of the patients had previous operative treatment, 6,7% (two of them) in stage I of the disease, 43,3% in stage II (13 patients) and half of the patients were in stage III of the disease (Table 1). The mean BMI was 27.32 ± 5.07 (19.2-38.6), and 26.7% of the patients were obese (Table 1). 53.3% had established HTA, 10% had DM type 2, and only 6,7% of the patients in the study had regular physical activity. One lady had heart failure (HF) with preserved LVEF%, classified NYHA class II. (Table 1).

All patients were treated according to the 4AC+taxol HT protocol, out of which 14 were at low and medium risk (46.7%) and 2 were at high risk (6.7%) for ATIC development. The mean range of the total AT dose was 403.13 ± 35.47 (320-480mg), and the mean indexed range was 220.53±12.64 (Table 1).

Table 1. Baseline characteristics of patients with breast cancer treated with anthracyclines (n=30)

Demographic and anthropometric data		**Parametars for the oncology therapy**	
Age (years)	52,5 ± 10,9 (34-76)	Opperative treatment (%)	96.7
Ethnicity(%)	macedon.60%; alban.23,3%; oth.16,7%	Radic.mastectomy with lymphadenectomy(%)	90,0
BMI (kg/m^2)	27,32 ± 5,07 (19,2-38,6)	Metastatic disease (%)	10
BSA (m^2)	1,82 ±0,17	Staging (%)	Ist 6,7; IIst 43,3, IIIst 50,0
Risk factor and associated diseases		Total AT dose (mg)	403,13±35,47 (320-480)
Obesity (%)	26,7	AT indexed dose (mg/m^2)	220,53±12,64 (191,6-247,0)
HTA (%)	53,3	AT risk(%)	low 46,7, moderate 46,7, high 6,7
DM (%)	10	**Clinical examination**	
Smoking (%)	40	BP (sist/diast) (mm/Hg)	131,0±18,4/ 77,8±9,6
Physical activity (%)	none 80, occasion.13,3, regular.6,7	Heart rate (beats/min)	78,9± 11,6
Familiar anamnesis for CVD (n/%)	26,7	Heart failure (n/%)	1/3,3 (NYHA II)
CKD (%)	3,3	QTc (msec)	403,37±21,10
COPD (%)	3,3		

AT anthracyclines, BMI body mass index, BSA body surface area, BP blood pressure, CKD chronic kidney disease, COPD chronic obstructive pulmonary disease, CVD cardiovascular disease, DM diabetes melitus, HTA hypertension, NYHA=New York Heart Association, QTc corrected QT interval, *Obesity= BMI ≥ 30 kg/m2

LV dimensions and volumes in diastole and systole during the first and second visit were within reference ranges (Table 2): for LV end-diastolic (LVDd) and LV end-systolic dimension (LVDs), as well as their values indexed for body surface area (LVDdI/LVDsI). However, the comparison of the values

between the two examinations presented a statistically significant increase in LVDd (p=0.026), while in LVDs, increasing was with borderline significance (p=0.055) (Table 2, Figure 1).

We also calculated the difference between the two visits in absolute numbers, and for LVDd we got a range of -1.23±3.08 mm, and for LVDs -0.86±2.28 mm.

Wall thickness values, interventricular septum (IVS) and posterior wall (PW) at both visits were within reference ranges, yet although they indicated a decrease at the control visit, the change was not statistically significant (p=0.816, p=0.864, respectively) (Table 2).

LV mass (LVM) taken as an absolute number and/or indexed for body surface area (LVMI) was within reference ranges at the baseline examination. During the second visit, there was an increase in both ranges, yet without a statistically significant change (p=0.210; p=0.214; consecutively). However, although the LVM presented ranges slightly above the reference as an absolute number, the LVMI remained within the reference ranges (Table 2). Relative wall thickness (RWT) presented that patients had LV with normal geometry (RWT≤ 0.42) which did not change significantly at the second visit (p=0.183) (table 2).

Table 2. Comparison of echocardiographic parameters of left ventricular internal dimensions and mass between the first and second examination in 30 subjects.

parameter	**I examination (n=30)**	**II examination (n=30)**	**p**
LVDd (mm)	48,97±3,05	50,20±3,08	**0,026**
LVDs (mm)	31,17±2,99	32,03±3,05	**0,055**
IVSd (mm)	9,57±1,59	9,53±1,45	0,816
PWd (mm)	8,67±1,24	8,63±1,29	0,864
LVM (g)	157,42±35,51	162,36±39,43	0,210
LVMI (g/m2)	86,24±16,94	89,07±18,93	0,214
RWT (mm)	0,35±0,04	0,33±0,05	0,183

LVDd left ventricular end-diastolic dimension, LVDs left ventricular end-systolic dimension, IVSd interventricular septum in diastole; PWd posterior wall in diastole; LVM left ventricular mass, LVMI left ventricular mass indexed for body surface area, RWT relative wall thickness, *p<0.05 for comparison between groups.

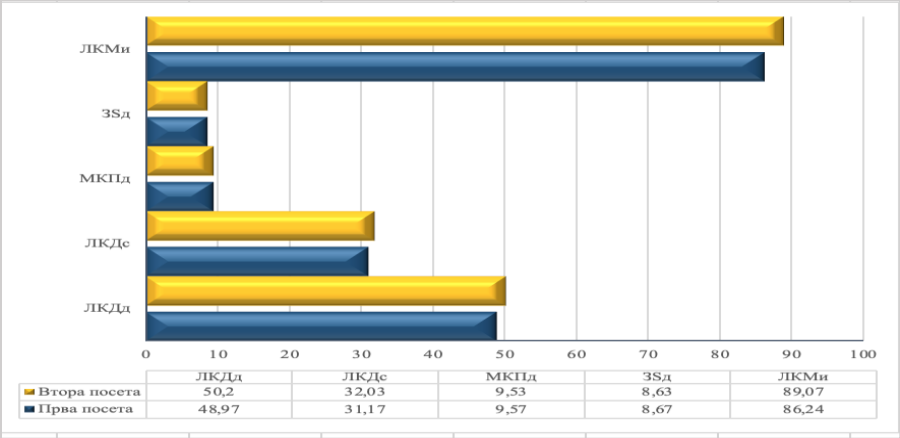

Figure 1. Graphic presentation of the internal dimensions change, wall thicknesses and indexed mass of the left ventricle during the first and second visit.

A correlation analysis of certain demographic parameters, risk factors, CV comorbidities and AT dose parameters with the echocardiographic measurments of LV dimensions, wall thicknesses and LV mass was performed and the results are presented in tables 3 and 4.

We found that increased LVDd had significant correlation with higher BMI, lower total AT dose and HTA at the second visit and lack of physical activity at both visits. With borderline significance increased LVDd was associated with higher AT risk at the second visit. (table 3)

Increased LVDs was significantly associated with older age, higher BMI, HTA, lack of physical activity and lower total AT dose at both visits (Table 3). Increased LVDs was significantly associated with obesity and higher AT risk at the second visit, while with borderline significance increased LVDs was associated with higher AT risk at the baseline visit (Table 3)

Higher IVSd thickness was significantly associated with older age, higher BMI, obesity, presence of DM, lower total AT dose and higher AT risk at both visits (Table 3). Higher IVSd thickness was also significantly associated with lack of physical activity at the first visit, and presence of HTA on the second visit. (table 3)

Higher PW thickness was significantly associated with older age, higher BMI, presence of HTA and DM, lack of physical activity and higher AT risk only at the second visit (table 4). Higher PW thickness was significantly associated with lower total AT dose at both visits(table 4)

Increased LVM was significantly associated with older age, higher BMI, HTA, lack of physical activity, lower AT dose and higher AT risk at both visits (table 4). Increased LVM was associated with presence of DM at the second examination with borderline significance (table 4)

Increased LVMI showed significant association with lower AT dose, higher AT risk, older age and presence of HTA on the control visit (table 4). At the baseline examination increased LVMI was significantly associated with lack of physical activity, and with borderline significance it was associated with older age at the baseline examination and with lack of physical activity at the control visit (table 4).

Higher RWT showed significant association only at the control exam. With absolute significance it was established with older age, presence of HTA and DM and higher AT risk (Table 4), while borderline significance was noticed with lack of physical activity (Table 4).

Table 3. Presentation of significant and borderline significant correlations of internal LV dimensions and wall thicknesses at the first and second visit

	LVDd1 (mm)	**LVDd2 (mm)**	**LVDs1 (mm)**	**LVDs2 (mm)**	**IVSd1 (mm)**	**IVSd2 (mm)**
age	-		r=0,503, p=0,003	r=0,606, p=0,0001	r=0,391, p=0,033	r=0,569, p=0,001
BMI	-	r=0,430, p=0,018	r=0,376, p=0,041	r=0,533, p=0,002	r=0,641, p=0,0001	r=0,465, p=0,010
HTA	-	r=0,3481, p=0,060	r=0,416, p=0,022	r=0,499, p=0,005	-	r=0,452, p=0,012
DM	-	-	-	-	r=0,377, p=0,040	r=0,497, p=0,05
obesity	-	-	-	r=0,368, p=0,045	r=0,408, p=0,025	r=0,362, p=0,049
Physical activit	r=-0,382, p=0,037	r=-0,394, p=0,031	r=-0,421, p=0,020	r=-0,469, p=0,009	r=-0,354, p=0,055	-
AT dose mg/m2	-	r=-0,599, p=0,0001	r=-0,355, p=0,054	r=-0,644, p=0,0001	r=-0,434, p=0,016	r=-0,385, p=0,036
AT risk		r=0,330, p=0,075	r=0,352, p=0,056	r=0,534, p=0,002	r=0,447, p=0,013	r=0,562, p=0,001

AT anthracyclines, LVDd left ventricular end-diastolic dimension; LVDs left ventricular end-systolic dimension; IVSd interventricular septum in diastole; BMI=body mass index; HTA hypertension; DM diabetes mellitus;

Table 4. Presentation of significant and borderline significant correlations of the LV mass and wall thicknesses at the first and second visit.

	PWd2 (mm)	**LVM1 (g)**	**LVM2 (g)**	**LVMI1 (g/m2)**	**LVMI2 (g/m2)**	**RWT2**
age	r=0,5151, p=0,004	r=0,401, p=0,028	r=0,578, p=0,001	r=0,343, p=0,063	r=0,556, p=0,001	r=0,372, p=0,043
BMI	r=0,421, p=0,020	r=0,511, p=0,004	r=0,504, p=0,005	-	-	-
HTA	r=0,516, p=0,004	r=0,385 p=0,036	r=0,499, p=0,005	-	r=0,371 p=0,044	r=0,368 p=0,045
DM	r=0,398, p=0,029	-	r=0,310, p=0,096	-	-	r=0,446, p=0,014
obesity	-	-	-	-	-	
Physical activit	r=-0,412, p=0,023	r=-0,456, p=0,011	r=-0,416, p=0,022	r=-0,412, p=0,024	r=-0,336, p=0,070	r=-0,328, p=0,077
AT dose mg/m2	r=-0,458, p=0,011	r=-0,387, p=0,035	r=-0,585, p=0,001	-	r=-0,466, p=0,009	
AT risk	r=0,504, p=0,004	r=0,419, p=0,021	r=0,564, p=0,001	-	r=0,414, p=0,023	r=0,378, p=0,039

AT anthracyclines, PWd posterior wall in diastole, LVM left ventricular mass, LVMI left ventricular mass indexed for body surface area, RWT relative wall thickness, BMI=body mass index; HTA hypertension; DM diabetes mellitus;

Given that there was a significant and borderline significant increase in LVDd and LVDs, subsequently (Table 3), we made a correlation analysis of the differences from the first and second examination for LVDd (-1.23±3.08) and LVDs (-0.86±2.28) with all demographic characteristics, risk factors and characteristics of oncology therapy and risk of ATIC, where we obtained a significant corelation of the increase only with the higher indexed total AT dose (mg/m2) (Figure 2 and 3).

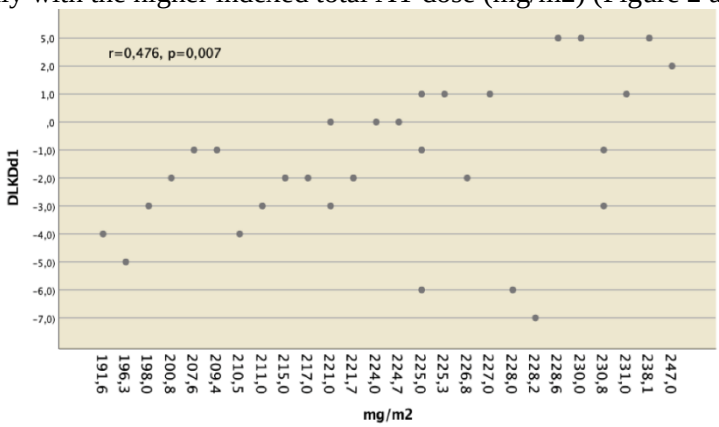

Figure 2. Graphic presentation of the correlation of the difference in the size of LVDd at the first and second visit with the total AT dose in mg/m2.

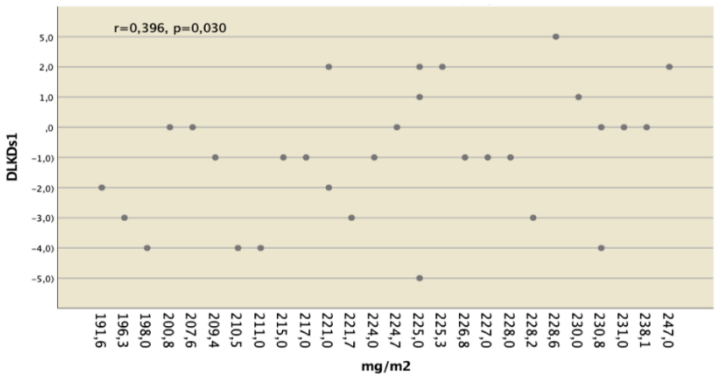

Figure 3. Graphic presentation of the correlation of the difference in the size of the LVDs at the first and second visit with the total AT dose in mg/m2.

We also made a linear regression analysis in which as dependent variables we entered the differences between the two visits for LVDd and LVDs, and as independent variables the demographic characteristics, risk factors, oncology therapy characteristics and the ATIC risk, whereby we found out that the higher indexed total AT dose (mg/m2) appeared as an independent predictor for the increase of both dimensions at the second visit.

At the same time, for each mg/m2 of the AT dose increase, there is an increase in the difference in LVDd between the two visits by 0.113mm (95% CI 0.029-0.196, p=0.010) (table 5, Figure 4)

Table 5. Gradual linear regression analysis of the LVDd difference between the first and second visit as a dependent variable and demographic characteristics, risk factors, oncology therapy characteristics and ATIC risk as independent variables where the total indexed AT dose emerged as a significant predictor.

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients			95.0% Confidence Interval for B	
		B	Std. Error	Beta	t	Sig.	Lower Bound	Upper Bound
1	(Constant)	-26,099)	9,019		-2,894)	,007	-44,573)	-7,625)
	mg/m2	,113	,041	,463	2,761	,010	,029	,196

a. Dependent Variable: DLKDd1

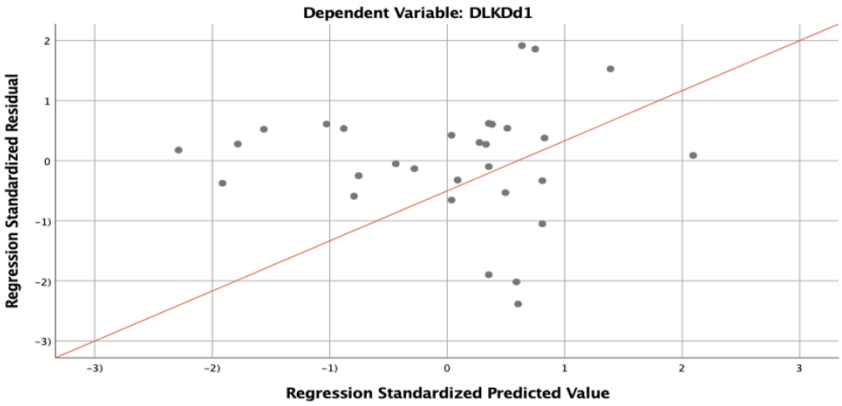

Figure 4. Graphic presentation of the linear regression analyses results from table 5.

For each mg/m2 of the AT dose increase, the difference in LVDs between the two visits increased by 0.071mm (95%CI 0.007-0.136, p=0.030) (table 6, Figure 5)

Table 6. Gradual linear regression analysis of the difference in LVDs between the first and second visit as a dependent variable and demographic characteristics, risk factors, oncology therapy characteristics and ATIC risk as independent variables where the total indexed AT dose emerged as a significant predictor.

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients			95.0% Confidence Interval for B	
		B	Std. Error	Beta	t	Sig.	Lower Bound	Upper Bound
1	(Constant)	−16,635)	6,930		−2,401)	,023	−30,829)	−2,440)
	mg/m2	,071	,031	,396	2,279	,030	,007	,136

a. Dependent Variable: DLKDs1

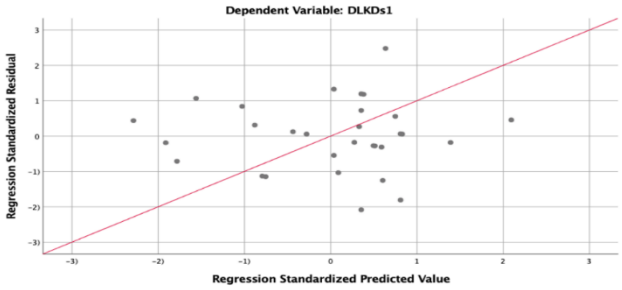

Figure 5. Graphical presentation of the linear regression analysis results from table 6.

Discussion

AT therapy is still the basic standard of anti-cancer therapy in patients with BC. The 2012 Early Breast Cancer Trialists' Collaborative Group in a meta-analysis of 100,000 women and 123 randomized studies demonstrated that AT-containing therapy regimens are superior over non-AT HT regimens and also AT containing-taxane combination regimens are superior vs. AT containing only in patients with early forms

of BC, with overall 36% reduced mortality [12]. San Antonio Breast Cancer Symposium (SABCS 2021) in a large meta-analysis comparing AT-taxane vs. monotaxane HT regimens presented 15% proportional reduction and 2,5% absolute reduction at 10 years of disease recurrence in patients with early stages BC taking combination regimens [95% confidence interval (CI) 0.9% to 4.2%] [13].

On the other hand, AT-induced long-term toxicities, mostly cardiac dysfunction and myelodysplastic syndromes points the question of careful risk-benefit evaluation and spaing AT-containing regimens for larger, more biologically agressive and node-postive BC patients, as the absolute benefit overwhelmes the risk and disease reccurence [14]. In a retrospective case-control study of 2196 subjects, of which 812 were patients with BC and lymphoma treated with ATs, the cumulative incidence of heart failure was 7.4% in 15 years follow-up compared to control groups and is twice as high, with a peak in the first year of exposure that persists over time [15].

Echocardiographic surveillance during AT-containing regimens are mandatory and close monitoring gives tremendous information for possible early cardiac disturbances as introduction to serious cardiac deteriorations [8].

Most of the studies are based upon a serial evaluation of LVEF%, strain evaluation and 3D changes. Changes in LV dimensions are presented not so frequent, mostly in a context of volume changes. Animal model study of doxorubicin in rats provokes echocardiographic changes similar to dilated cardiomyopathy, showing increased LV systolic (5.02 ± 0.96 mm) and diastolic (7.68 ± 0.96 mm) dimension, as well as LVEF% reduction in the group sample treated with more total cumulative doxorubicin doses vs. smaller portions and/or control groups[16]. A case-contol study in a pediatric population with at least 12 months AT therapy showed significant changes in wall thicknesses i.e. lower diastolic and systolic IVS and PW thickness, as well as increased LV internal systolic dimension and decreased LV mass index in patients treated with ATs [17]. Increased LVDs was also associated with total cumulative AT dose. According to LV mass numerous studies mostly witness that AT exposure induce decline in LV mass due to myocellular and mitochondrial injury, myocellular apoptosis and atrophy and LV remodeling (20) and decrements in LV mass is associated with HF worsening independent of LVEF% reduction. (19) Cardiac magnetic resonance studies further claim that people receiving higher doses of ATs have lower indexed LV mass and in patients with established AT-induced cardiomyopathy is a predictor of adverse CV events [18].

In our study, the increase in LVDd at the second examination was statistically significant, while the increase in LVDs was borderline significant. Changes in other parameters did not show any statistical significance in our study, but futher examinations are needed (table 2)

The association of certain demographic parameters, multiple comorbidities, dietary and lifestyle habits with an increased ATIC risk is always a hot topic, trying to find the best conditions where toxic cancer therapy will be safe. From female gender, advanced age and cumulative AT dose as greatest risk factors for ATIC [21], to studies where therapies with antioxidative properties like vit. E can have favorable effects in preventing LV myocardial dysfunction, integrative approach for overall good outcome is ideal formula [22]. The American Heart Association publishes the first scientific report in which CVD and BC share common risk factors, so prevention and treatment of CVD in these patients stays the main goal for mitigating negative effects of cancer therapy on CV health [23].

Obesity and overweight increase the risk for ATIC in BC patients and females with lower BMI experience lower risk of adverse toxic effects [25]. In the same time high-fat diets and serum hyperlipidemia make patients susceptible to AT cardiotoxicity due to higher level of oxidative stress and elevated levels of intracellular reactive oxygen species [26]. Elevated BP and HTA are known risk for alleviating and deteriorating HF. In conditions of already potential cardiotoxic milieu, elevated BP plays significant role in ATIC presentation, even without previous CV anamnesis. In a meta-analysis of 12 studies in young patients, HTA showed increased vulnerability for AT cardiotoxicity in patients with elevated BP before cancer therapy as independent predictor [28]. Studies in Ren-2 transgenic rats presented accentuated toxic AT effects even in rats genetically predisposed to develop hypertension combined to cardiomyopathy due to hyperactivity of renin-angiotensin system [27].

Recently published meta-analyses of total of 33 studies in over 55700 BC patients, reveale that diabetes, along with other risk factors from Framingham risk score was associated with increased risk of cardiac events and reported cardiotoxicity [30]. A nine-year retrospective study in BC patients who developed cardiomyopathy, DM was found significantly associated with an increased risk of ATIC. [29]. Excercise training is still a question of debate if it significantlly affects cardiac toxicity prevention [32], but regular physical activity for sure improves CV reserve, cardiorespiratiry fitness and psychosocial and physical function outcome and is safe and recommended during and after cardiotoxic cancer treatment. (31)

In our study, the correlation of the differences of the first and second visits of LVDd and LVDs indicated a significant association with a higher indexed total AT dose. A higher indexed AT dose appeared as an independent predictor of an increase in LVDd and LVDs at the second visit.

Conclusion

In conclusion, results from this study confirm that ATs induce frequent changes in echocardiographic parameters in patients with BC. Increased LV dimensions showed significant association with total, cumulative AT dose indexed for body surface area, as a strongest risk factor for induced cardiotoxicity occurence. Higher, cumulative AT dose is an independent predictor for the increase of LV dimensions during AT cancer therapy.

References

1. Breast Cancer Statistics | How Common Is Breast Cancer? | American Cancer Society. (n.d.). https://www.cancer.org/cancer/types/breast-cancer/about/how-common-is-breast-cancer.html
2. Willis, M. S., Parry, T. L., Brown, D. I., Mota, R. I., et al. (2019). Doxorubicin exposure causes subacute cardiac atrophy dependent on the striated muscle–specific ubiquitin ligase MURF1. *Circ Heart Fail, 12*(3). https://doi.org/10.1161/circheartfailure.118.005234
3. American Cancer Society. Breast Cancer Facts & Figures 2022-2024. Atlanta: American Cancer Society, Inc.2022
4. Lancellotti, P., Suter, T. M., López-Fernández, T., Galderisi, M., Lyon, A. R., Van der Meer, P., et al. (2018). Cardio-Oncology Services: Rationale, organization, and implementation. *Eur Heart J, 40*(22), 1756–1763. https://doi.org/10.1093/eurheartj/ehy453
5. Cancer of the breast (female) - cancer stat facts. SEER. (n.d.). Retrieved 01.31.2023 from https://seer.cancer.gov/statfacts/html/breast.html
6. Lyon, A.R., López-Fernández, T., Couch, L. S., et al. 2022 ESC guidelines on cardio-oncology developed in collaboration with European Hematology Association, European Society for Therapeutic Radiology and Oncology and International Cardio-Oncology Society. *Eur. Heart J.*, *43* (41), 4229–4361
7. Cardinale, D., Iacopo, F., & Cipolla. C. M. et al. (2020) Cardiotoxicity of Anthracyclines. *Front Cardiovasc Med*, *7*.
8. Čelutkienė, J., Pudil, R., López-Fernández, T., et al. (2020) Role of cardiovascular imaging in cancer patients receiving cardiotoxic therapies: A position statement on behalf of the Heart Failure association, European association of Cardiovasc. Imaging and cardio-oncology Council of ESC *Eur.J.Heart Fail*.,22(9),1504–1524
9. Lyon, A. R., Dent, S., Stanway, S., et al. (2020). Baseline cardiovascular risk assessment in cancer patients scheduled to receive cardiotoxic cancer therapies: A position statement and new risk assessment tools from the Cardio-Oncology study Group of the Heart Failure Association of the ESC in collaboration with the International Cardio- Oncology society. *Eur. J. Heart Fail.*, 22(11), 1945–1960.
10. Zamorano, J. L., Lancellotti, P., Rodriguez Muñoz, D. et al. 2016 ESC position paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines. *Eur. Heart J.*, 37(36), 2768–2801.

11. Lang, R. M., Badano, L. P., Mor-Avi, V., Afilalo, J., et al. (2015) Recommendations for cardiac chamber quantification by echocardiography in adults: An update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*, *28*(1). https://doi.org/10.1016/j.echo.2014.10.003
12. Early Breast Cancer Trialists' Collaborative Group (2012) Comparisons between different polychemotherapy regimens for early breast cancer: Meta-analyses of long-term outcome among 100 000 women in 123 randomised trials. *The Lancet*, *379*(9814), 432–444.
13. Braybrooke, J., Bradley, R., Gray, R., et al. (2023). Anthracycline-containing and Taxane-containing chemotherapy for early-stage operable breast cancer: A patient-level meta-analysis of 100 000 women from 86 randomised trials. *The Lancet*, *401*(10384), 1277–1292.
14. Guarneri, V., & de Azambuja, E. (2022). Anthracyclines in the treatment of patients with early breast cancer. *ESMO Open*, *7*(3), 100461. https://doi.org/10.1016/j.esmoop.2022.100461
15. Larsen. C. M., Garcia Arango, M., Dasari, H et al. (2023) Association of anthracycline with heart failure in patients treated for breast cancer or lymphoma,1985-2010.*JAMA*, *6* (2)
16. O'Connell, J. L., Romano, M. M., Campos Pulici, E. C., et al. (2017). Short-term and long-term models of doxorubicin-induced cardiomyopathy in rats: A comparison of functional and histopathological changes. *Exp Toxicol Pathol*, *69*(4), 213–219. https://doi.org/10.1016/j.etp. 2017.01.004
17. Iarussi, D, Galderisi, M, Ratti, G. et al (2001) Left ventricular systolic and diastolic function after anthracycline chemotherapy in childhood. *Clin Cardiol*, *24*(10), 663–669. https://doi.org/10.1002/clc.4960241006
18. Neilan, T. G., Coelho-Filho, O. R., Pena-Herrera, D., Shah, R. V., et al. (2012). Left ventricular mass in patients with a cardiomyopathy after treatment with anthracyclines. *Am J Cardiol*, *110*(11), 1679–1686. https://doi.org/10.1016/j.amjcard.2012.07.040
19. Jordan, J. H., Castellino, S. M., Meléndez, G. C., et al. (2018). Left ventricular mass change after anthracycline chemotherapy. *Circ Heart Fail*, *11*(7).
20. Ferreira de Souza, T., Quinaglia. A. C. Silva, T., et al. (2018) Anthracycline therapy is associated with cardiomyocyte atrophy and preclinical manifestations of heart disease. *JACC Cardiovasc Imaging.11*(8), 1045–1055
21. Volkova, M., & Russell, R. (2012) Anthracycline cardiotoxicity: Prevalence, pathogenesis and treatment. *Curr Cardiol Rev*, *7*(4), 214–220. https://doi.org/10.2174/157340311799960645
22. Berthiaume, J. M., Oliveira, P. J., Fariss, M. W., & Wallace, K. B. (2005). Dietary vitamin E decreases doxorubicin- induced oxidative stress without preventing mitochondrial dysfunction. *Cardiovasc Toxicol*, *5*(3), 257–268. https://doi.org/10.1385/ct:5:3:257
23. Mehta, L. S., Watson, K. E., Barac, A., Beckie, T. M., et al. (2018). Cardiovascular disease and breast cancer: Where these entities intersect: A scientific statement from the American Heart Association. *Circulation*, *137*(8). https://doi.org/10.1161/cir.0000000000000556
24. Guenancia, C., Lefebvre, A., Cardinale, D., et al. (2016). Obesity as a risk factor for anthracyclines and trastuzumab cardiotoxicity in breast cancer: A systematic review and meta-analysis. *JCO*, *34*(26), 3157–3165.
25. de Azambuja, E., McCaskill-Stevens, W., Francis, P. et al. (2009) The effect of body mass index on overall and disease-free survival in node-positive breast cancer patients treated with docetaxel and doxorubicin-containing adjuvant chemotherapy: The experience of 02-98 trial. *Breast Cancer Res Treat*, *119*(1),145–153.
26. Mitra, M., Donthamsetty, S., White, B., & Mehendale, H. (2008). High fat diet-fed obese rats are highly sensitive to doxorubicin-induced cardiotoxicity. *Toxicol Appl Pharmacol*, *231*(3), 413–422. https://doi.org/10.1016/j.taap.2008.05.006
27. Kala, P., Bartušková, H., Piťha, J., et al. (2020). Deleterious effects of hyperactivity of the renin-angiotensin system and hypertension on the course of chemotherapy-induced heart failure after

doxorubicin administration: A study in ren-2 transgenic rat. *Int J Mol Sci*, *21*(24), 9337. https://doi.org/10.3390/ijms21249337

28. Philip, L. J., Findlay, S. G., & Gill, J. H. (2022). Baseline blood pressure and development of cardiotoxicity in patients treated with anthracyclines: A systematic review. *Int J Cardiol Cardiovasc Risk Prev*, *15*, 200153.
29. Reinbolt, R. E., Patel, R., Pan, X., et al. (2015). Risk factors for anthracycline-associated cardiotoxicity. *Support Care Cancer*, *24*(5), 2173–2180.
30. Jin, H., Xu, J., Sui, Z., & Wang, L. (2023). Risk factors from Framingham risk score for anthracyclines cardiotoxicity in breast cancer: A systematic review and meta-analysis. *Front Cardiovasc Med*, *10*. https://doi.org/10.3389/fcvm.2023.1101585
31. Kang, D.-W., Wilson, R. L., Christopher, C. N., et al. (2022) Exercise as a potential therapeutic modality in the management of anthracycline-induced cardiotoxicity. *Front Cardiovasc Med*, *8*.
32. Antunes, P., Joaquim, A., Sampaio, F., et al. (2023). Effects of exercise training on cardiac toxicity markers in women with breast cancer undergoing chemotherapy with anthracyclines: A randomized controlled trial. *Eur J Prev Cardiol*, *30*(9), 844–855.