Original Paper

Risk Factors for Anthracycline Associated Cardiotoxicity in Iraqi Breast Cancer Patients

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Abstract

Background: Anthracyclines are among the most successful medicines for treating breast cancer; when taken in combination regimens, they enhance both disease-free and overall survival in breast cancer patients. Unfortunately, they are the representative agents causing cardiotoxicity, particularly Left ventricular dysfunction**.**
Aim of the study: To assess the incidence and risk factors for anthracycline-induced cardiotoxicity for early detection and prevention among breast cancer patients**.**
Methods: Eighty-six patients with breast cancer were given Adriamycin (60 mg/ m2) with cyclophosphamide (600 mg/m2), with different cycles number and frequencies. They were prospectively monitored clinically, and by echo study to detect any cardiotoxicity, several patients and drug-related risk factors were analyzed to identify their influence on Anthracycline Induced Cardiotoxicity.
Results: After anthracycline chemotherapy, 21 patients (24.4%) developed diastolic dysfunction, and 7 patients (8.1%) developed reduction in the left ventricular ejection fraction more than 10%, out of these 7 patients, 4 developed symptomatic cardio toxicity. Older age (> 60 years), Hypertension, diabetes, and abnormal renal function were all associated with a higher risk for developing anthracycline cardiotoxicity.
Conclusions: Cardiotoxicity is common among breast cancer patients treated with anthracycline-based chemotherapy, which can even occur in a dose less than 240mg/m2. Age older than 60, Hypertension, diabetes mellites, and abnormal renal function showed significant association with Anthracycline Induced Cardiotoxicity.
Keywords: breast cancer, anthracycline, cardiotoxicity.

Introduction

Breast cancer is the world's most diagnosed malignancy and the top cause of female death [(1)]. In Iraq, according to the latest registration of Iraqi cancers, breast cancer is the most common type of cancer in general (19.55%) and among women, accounting for (34.27%), and it accounts for the highest cancer mortality in females [(2)]. The systemic treatment usage and the introduction of screening mammography have contributed to an increase in the survival of these individuals in recent decades [(3)]. Systemic treatment aims to prevent breast cancer recurrence by removing hidden, micrometastatic tumor deposits present at the time of curative surgery. Three systemic therapy methods are commonly utilized in contemporary practice. Endocrine therapies, anti-HER2 therapy, and chemotherapy are among the options. [(4)]. Four cycles of Adriamycin (60 mg/ m2) with cyclophosphamide (600 mg/ m2; AC) are the cornerstone and commonly used adjuvant therapy for patients with primary breast cancer in current breast cancer treatment [(5)]. This regimen improves disease-free and overall survival considerably, especially when used with paclitaxel. Adriamycin (Doxorubicin), on the other hand, is potentially cardiotoxic, causing permanent and dose-dependent

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myocardial damage. Because adjuvant therapy is used to cure patients, the benefits must balance the dangers of short- and long-term toxicity [6].

Anthracyclines have a flat, planar structure and are relatively hydrophobic. Their quinone structure promotes the production of oxygen free radicals, which may be implicated in anticancer activities as well as the cardiotoxicity associated with these medicines [7]. The incidence of cardiac failure with the (AC) regimen is around 1.6 percent, rising to roughly 2.1 percent in patients who take doxorubicin followed by paclitaxel. However, doctors are confronted with additional issues such as asymptomatic ventricular failure, diastolic dysfunction, and cardiovascular events in long-term survivors [8]. As a result, even in asymptomatic individuals, early referral to a cardiologist is suggested in the case of suspected cardiotoxicity because mounting evidence shows that medical treatment may delay disease development [9].

This study aimed to assess the incidence and risk factors for anthracycline-induced cardiotoxicity (AIC) for early detection and prevention among breast cancer patients**.**

Patients and Methods

Study population: This prospective observational study was conducted at Oncology teaching hospital/Baghdad medical city from April 1st to September 30th, 2019. All 86 female patients with histologically confirmed breast cancer at any stage and tumor biology were included and prospectively followed.

The study was authorized by the scientific council of the Iraqi board of medicine, and all patients who participated in it gave verbal consent. Data and patient privacy was kept confidential.

Chemotherapy protocol

All cases received chemotherapy protocol [Doxorubicin 60mg/m2 + Cyclophosphamide 600mg/m2 (AC)]. with different cycles number (from 1-6 cycles) and frequency (every 3 weeks or every 2 weeks). Doxorubicin had been administered by IV infusion in 200 ml normal saline for 30 min with close observation at Oncology teaching hospital.

Cardiac assessment

All patients underwent clinical assessment pre-and post-chemotherapy, including heart-related history and examination. An electrocardiograph (ECG) was conducted for each patient before starting chemotherapy (at baseline) and after completion of all cycles. The same cardiologists did a 2-dimensional transthoracic echo study for each patient before starting chemotherapy and after 3 weeks of completion of all cycles to assess the cardiac function by assessing Left ventricular systolic and diastolic volumes and ejection fraction (EF%) (to detect any decline in the EF% below the baseline, diastolic dysfunction, new valvular disease, pericardial effusion, and other heart diseases).

Criteria used to diagnose Cardiac dysfunction due to doxorubicin

(1) Symptoms or signs associated with heart failure (HF)

(2) A decrease in left ventricular ejection fraction (LVEF) of at least 5 to <55 percent in the presence of HF signs or symptoms, or a decrease in LVEF of ≥10 to <55 percent in the absence of HF signs or symptoms [10].

(3) Development of diastolic dysfunction.

Data collection

Several patients and drug-related risk factors were analyzed to identify their influence on AIC, including (age, BMI, Hypertension (HT), diabetes mellitus (DM), smoking, renal and liver function status, and Hb. level). Tumor-related factors, including (tumor biology, stage, and side) were also analyzed.

Exclusion criteria:

1. Female age < 18 years
2. Previous anthracycline exposure.
3. Patients with a pre-exposure history of heart disease, including:

a. Myocardial infarction
b. Myocarditis
c. Pericardial effusion.
d. Congestive heart failure.

e. Valvular heart disease requires treatment.
f. Arrhythmia with clinical significance.
g. Significantly abnormal ECHO study

Statistical analysis

The Statistical Package for Social Sciences (SPSS) version 25 was used to analyze the data. The data is given in a mean, standard deviation, and ranges. Categorical data is given in the form of frequencies and percentages. The continuous variables were compared using an independent t-test (two-tailed), and the Chi-squared test was performed to evaluate the relationship between anthracycline cardiotoxicity and specific information. A level of P-value of 0.05 or less was considered significant.

Results

A total of eighty-six individuals were chosen for this investigation. The participants' ages varied from 28 to 80 years old, with a mean of 52 years and an SD of 11 years. More than half of the patients (59.3%) were between 40 and 60. BSA levels ranged from 1.4 to 2 m2, with a mean of 1.73 and a standard deviation of 0.16.

Clinical presentation related to cardiotoxicity

Among the 86 recruited patients,82 (95.2%) had no relevant complaints. On the other hand, one patient complained of chest pain and another one of palpitation, while myocarditis and pericardial effusion were found in another patient (Fig.1)

ECG Findings

ECG abnormalities were recorded in 4 patients as follows: sinus tachycardia (having a heart rate of more than 100 beats per minute (bpm) with sinus rhythm) in 2 patients (2.3%), ST depression (the trace in the ST segment is abnormally low below the baseline.) in another one, and low voltage QRS complex (All limb leads have a QRS voltage of less than 5 mm, and all precordial leads have a QRS voltage of less than 10 mm.), in a fourth (11), (Fig. 2).

Echo Findings

After anthracycline chemotherapy, 21 patients (24.4%) developed diastolic dysfunction, and 7 patients (8.1%) developed cardiotoxicity according to the definitions of cardiac review and evaluation committee (12). one of the patients developed myocarditis, another got pericardial effusion, and a third got tricuspid valve regurgitation (TR) with decreased EF%. the other 4 patients developed an asymptomatic decrease in the EF% more than 10% below baseline. The remaining 58 patients (67.4%) revealed normal Echo results (Fig. 3).

The Association Between Anthracycline Cardiotoxicity considered Factors:

Table (1) shows the association between anthracycline cardiotoxicity and certain demographic data of patients. It was clear that older age (> 60 years) was a significant risk factor (P= 0.014) for developing cardiotoxicity after anthracycline chemotherapy, as more than half of patients of this age group got some degree of cardiotoxicity. No significant influence was found for BMI nor smoking (P=0.389, 0.389 respectively) on AIC.

Comorbidities

HT, DM, and abnormal renal function (RF) were all associated with a higher risk of developing anthracycline cardiotoxicity (P= 0.001, 0.001,0.011). On the other hand, neither anemia (Hb<12mg/dl) nor thyroid function status showed such an influence on the cardiotoxicity of anthracycline treatment (Table 2).

Breast Tumor characteristics

There is no significant association between the AIC with tumor side, stages, hormone receptor status, and Her2neu receptor status (P= 0.351, 0.982, 0.192, and 0.287), respectively (Table 3).

Discussion

In recent decades, improvements in breast cancer patient survival and chemotherapy toxicity have resulted in a rise in the frequency of cardiovascular morbidity in these patients. Although anthracyclines are very efficient antitumor drugs and are still an important part of many chemotherapy regimens, their cardiotoxicity has a major

influence on patient health and quality of life, hence the potential usefulness of this study.

Most research indicated that treatment with Doxorubicin might cause heart damage, especially if the cumulative dosage is greater than 300 mg/m2 [13]. however, In the current study, it was found that LV systolic dysfunction can develop in lower cumulative doses ranging from 60mg/m2-240mg/m2 (1-4 cycles of AC protocol), with an incidence of 8.2%, which was similar to the findings by Perez et al. [14]. Who studied the development of cardiotoxicity by doing an echo study after 3 weeks from the end of the 4th cycle of Doxorubicin plus cyclophosphamide chemotherapy (AC) in breast cancer patients and found that a cumulative dose of 240mg/m2 can induce cardiotoxicity.

Also, in the current study, the LV diastolic dysfunction was used as an early sign of cardiotoxicity, which preceded the reduction in the LV EF%. with an incidence of 24.4%—based on results by Lee et al. [15], Who identified diastolic dysfunction as an early sign of doxorubicin cardiotoxicity with serial radionuclide angiography prior to the development of LV systolic dysfunction in patients taking Doxorubicin. Reports of early diastolic dysfunction with an incidence range of (15-57%) soon followed this observation using Doppler echocardiography of LV filling dynamics during doxorubicin treatment [16].

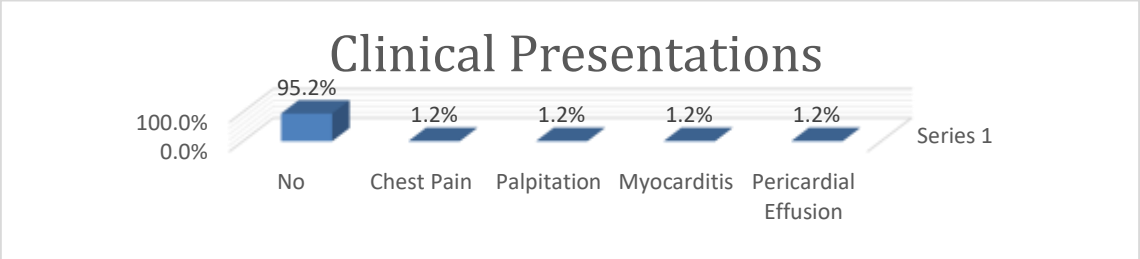

Figure 1. Distribution of patients according to their clinical presentations

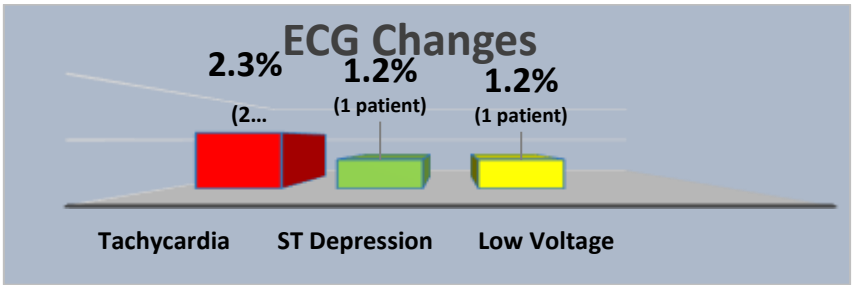

Figure 2. Distribution of patients according to ECG findings

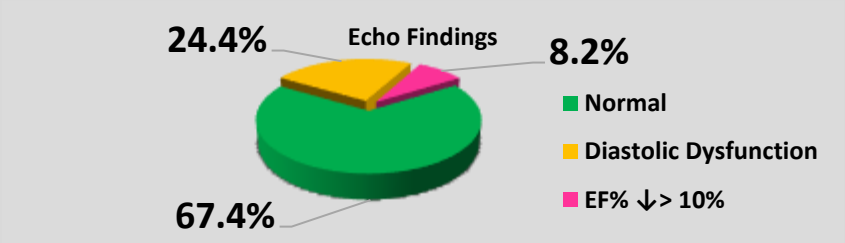

Figure 3. Echo findings of study patients after chemotherapy

Table 1. Association of anthracycline cardiotoxicity with age, BMI level, and smoking status

Variable	Anthracycline Cardiotoxicity		Total (%) n= 86	P- Value
	Yes (%) n= 28	**No (%) n= 58**		
Age (Years)				
< 40	2 (14.3)	12 (85.7)	14 (16.3)	**0.014**
40 - 60	14 (27.5)	37 (72.5)	51 (59.3)	
> 60	12 (57.1)	9 (42.9)	21 (24.4)	
BMI Level (Kg/m2)				
Normal (18.5-24.9)	6 (40.0)	9 (60.0)	15 (17.4)	**0.389**
Overweight (25-29.9)	10 (40.0)	15 (60.0)	25 (29.1)	
Obese (> 30)	12 (26.1)	34 (73.9)	46 (53.5)	
Smoking				
Yes	5 (83.3)	1 (16.7)	6 (7.0)	**0.389**
No	23 (28.7)	57 (71.3)	80 (93.0)	

Table 2. Association between anthracycline cardiotoxicity and patient's comorbidities

Variable	Anthracycline Cardiotoxicity		Total (%) n= 86	P- Value
	Yes (%) n= 28	**No (%) n= 58**		
HT				
Yes	23 (69.7)	10 (30.3)	33 (38.4)	**0.001**
No	5 (9.4)	48 (90.6)	53 (61.6)	
DM				
Yes	10 (71.4)	4 (28.6)	14 (16.3)	**0.001**
No	18 (25.0)	54 (75.0)	72 (83.7)	
Abnormal RF				
Yes	3 (100.0)	0 (0)	3 (3.5)	**0.011**
No	25 (30.1)	58 (69.9)	83 (96.5)	
Hb<12mg/dl				
Low	2 (66.7)	1 (33.3)	3 (3.5)	**0.199**
Normal	26 (31.3)	57 (68.7)	83 (96.5)	
Hyper-thyroid				
Yes	1 (33.3)	2 (66.6)	3 (3.5)	**0.976**
No	27 (32.5)	56 (67.5)	83 (96.5)	
Hypo-thyroid				
Yes	2 (66.6)	1 (33.3)	3 (3.5)	**0.199**
No	26 (31.3)	57 (68.7)	83 (96.5)	

Table 3. Association between anthracycline cardiotoxicity and details of breast cancer

Variable	Anthracycline Cardiotoxicity		Total (%) n= 86	P- Value
	Yes (%) n= 28	**No (%) n= 58**		
Side				
Left	11 (27.5)	29 (72.5)	40 (46.5)	**0.351**
Right	17 (37.0)	29 (63.0)	46 (53.5)	
Stage				
One	1 (25.0)	3 (75.0)	4 (4.7)	**0.982**
Two	12 (31.6)	26 (68.4)	38 (44.2)	
Three	14 (34.1)	27 (65.9)	41 (47.6)	
Four	1 (33.3)	2 (66.7)	3 (3.5)	
ER, PR Receptors				
Positive	18 (28.6)	45 (71.4)	63 (73.3)	**0.192**
Negative	10 (43.5)	13 (56.5)	23 (26.7)	
Her2neu Receptors				
Positive	15 (38.5)	24 (61.5)	39 (45.3)	**0.287**
Negative	13 (27.7)	34 (72.3)	47 (54.7)	

Regarding the influence of the different risk factors for Adriamycin-induced cardiotoxicity (AIC), it was found that older age (> 60 years) developed AIC significantly more than other age groups (P= 0.014), which was comparable with multiple studies done by the American society of clinical oncology, mainly the study by Armenian et al. [17]. Swain et al. also found a 2.25-fold increase in the risk of cardiotoxicity in women older than 65 years but with cumulative doxorubicin dose >400mg/m2 [18].

In the current study, HT and DM were linked to a greater risk of anthracycline cardiotoxicity (P= 0.001, 0.001), which is comparable to Ryberg et al. findings [19], who found that patients having preexisting hypertension, diabetes, or other cardiac risk factors had 3 times higher incidence of developing AIC, which was not related to the cumulative dose. The mechanism behind the effect of HT on anthracycline cardiotoxicity was identified by a Korean study on hypertensive rats [20], reporting that HT is a definite risk factor for doxorubicin-induced cardiotoxicity.

In addition to HT and diabetes, Ryberg et al. found that thyrotoxicosis and obesity were significant cardiac risk factors for AIC [19]. However, in the current study, neither BMI nor thyroid status significantly affected cardiotoxicity.

In the current study, abnormal renal function is significantly associated with cardiotoxicity (P=0.011). This finding is comparable to Russo et al. [21], who reported that renal function is an additional risk factor for chemotherapy-induced cardiotoxicity based on the heart kidney axis effect.

Also, in the current study, Hb did not influence AIC (P= 0.199), which may reflect the correction of low Hb for every patient planning to receive chemotherapy. As well as there was no significant association between the AIC with tumor side, stages, hormone receptor status, and Her2neu receptor status (P= 0.351, 0.982, 0.192, and 0.287), respectively. No previous studies showed any significant effects of these factors apart from the tumor side since long-term breast cancer irradiation survivors with left-sided tumors in randomized trials showed a 34% increased risk of mortality from cardiotoxicity compared to right-sided tumors [22]. However, radiotherapy was not included in this study.

Conclusions

The current study showed that cardiotoxicity is common among breast cancer patients treated with anthracycline-based chemotherapy (AC. Protocol) even with a cumulative dose as low as 240mg/m2. Thus, Echo studies should be conducted on all patients with breast cancer before and after receiving all cycles of the chemotherapy regimen. Age older than 60, Hypertension, diabetes mellites, and abnormal renal function showed significant association with AIC, so more consideration is required for these patients.

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