Cardiac Effect of Trastuzumab on Breast Cancer Women at Oncology Teaching Hospital / in Baghdad, Iraq

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Abstract

Breast cancer is first of the top ten malignancies in Iraq, accounting more than one-quarter of female cancers in the Iraqi. Treatment of cardiotoxicity induced by trastuzumab significantly reducing the clinical manifestations of cardiac dysfunction. The study aimed to described human epidermal growth factor receptor 2 positive non metastatic breast cancer among Iraqi female patients, and analyzed of cardiac monitoring by echocardiograph studies in their adjuvant setting. In addition, assessment of cardiac adverse effects related to trastuzumab treatment. A retrospective longitudinal study of 142 non-metastatic breast cancer females were included, at Oncology Teaching hospital/ Medical City Teaching Complex, Baghdad, Iraq, from 1 December 2018 to 30 November 2019. The adequacy of cardiac monitoring was determined by echocardiograph study at first setting before first dose of trastuzumab, 12 weeks , and 24 weeks sequel. The mean women age of the study was 53.54±10.058 years with median age of 54.5 years. The mean was 1.81±0.34 m^2 with median of 1.65 m^2. Regarding BMI, the mean was 30.62±5.51 m^2/Kg with median of 30.05 m^2/Kg. The most common stage of breast cancer in the study was stage IIIA 33(24.6%) patients, followed by stage IIA 31(23.1%) patients, and stage IIB 30(22.4%) patients. Regarding TNM staging of breast cancer, the tumor size 20 – 50 mm (T2) stage was common 94(70.1%), and the results showed a high frequency of no lymph node metastasis (N0) staging in 49(36.8%). Anthracyclin AC protocol given to 117(82.3%) patients, and taxen given to 113(79.5%) patients. A total of 106(74.6%) of women underwent mastectomy, while the rest 36(25.4%) underwent breast conservative surgery. Women received radiotherapy were 81(57.7%), whereas 60(42.3%) weren't. Hormonal therapy like Aromatase inhibitors received by 20(14.1%) patients, while 49(34.5%) of females were on tamoxifen. Most of females 134(92.2%), received trastuzumab as 17 doses (dose every 21 days for one year duration). 8(5.6%) females stopped trastuzumab and didn't complete protocol due to developing of cardiac toxicity after 6; 7; 8; 10; 11, doses. Baseline cardiac evaluation was performed in 139(97.8%) of patients by echocardiography 1; 141(99.3%) had an echocardiography 2 study within the first 12 weeks of trastuzumab therapy, and 138(97.2%) of patients done echocardiography 3 study at 24 weeks of therapy. Normal echocardiograph 1 study in 123(86.6%) patients were ejection fraction (EF) =55-70%. Normal EF% (>55%) plus abnormal findings presented in 14(9.8%), 30(21.1%), and 27(19%) of patients. The abnormal EF% (50%) plus abnormal findings noticed in 1(0.7%), 3(2.1%), and 3(2.1%) patients. Abnormal EF% (<50%; 40%; 30%; <30%) plus abnormal findings were observed 1(0.7%), 9(6.3%), and 14(9.8) of patients, with strongly significant reduction rate 41.7% in EF% at ($p<0.000$). Cardiac assessment, and heart function measurement, including EF measurement, performing before chemotherapy is a baseline guide in frequent assessment in the future. Cardiac risk factors management like hypertension before the first cycle of chemotherapy is mandatory. Reassessment of EF after completing chemotherapy and before starting trastuzumab, and repeat measurements throughout therapy is of great value in preventing decline in health status.

Keywords: Breast cancer; Herceptin; Ejection fraction; Cardiac toxicity

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Introduction

Breast cancer (BC) is the most common cancer in women, and it is estimated that one in eight women in the US will develop BC in their lifetime; also, the leading cancer among women in both Europe and US and becoming an emerging oncologic disease in developing countries; and every year, more than 500,000 women die from BC, making it the second leading cause of cancer mortality (Murthy et al., 2016). In Iraq there were 3845 cases estimated at 2011 (ICR, 2011), but this number reached 4542 in 2014 according to WHO (WHO, 2014).

BC therapy require a multidisciplinary team consisting of surgeons, medical oncologists, radiation oncologists, pathologists, radiologists, reconstructive surgeons, and supportive care personnel; where, most patients with BC receive surgery, radiation, and systemic treatment, and each component of these treatments has been shown to independently offer survival benefit for selected patients (Murthy et al., 2016).

Trastuzumab is a recombinant DNA-derived humanized monoclonal antibody that selectively bind with high affinity in a cell-based assay (Kd=5 nM) to the extracellular domain of the human epidermal growth factor receptor 2 protein (HER2) (or c-erbB2) proto-oncogene, which encode a trans-membrane receptor protein of 185kDa, and it is structurally related to the epidermal growth factor receptor (Coussens et al., 1985). The chemical formula of trastuzumab is $C_{6470}H_{10012}N_{1726}O_{2013}S_{42}$ and the average weight of it is 145531.5 Dalton (Da) (FDA, 2019, www.DrugBank.ca). HER2 protein overexpression is observed in 25%–30% of primary BC, and can be determined using an IHC based assessment of fixed tumor blocks (Baselga et al., 1998; Lewis et al., 1993). Trastuzumab used in combination with anthracycline plus cyclophosphamide (Boekhout et al., 2011; Leveque et al., 2008; Albanell et al., 2003; Treish et al., 2000).

Dyspnea, increased cough, paroxysmal nocturnal dyspnea, peripheral edema, S3 gallop, or reduced ejection fraction (EF) are signs and symptoms of cardiac toxicity, which recorded in patients treated with trastuzumab. Thus may be severe and has been associated with disabling cardiac failure, death, and mural thrombosis leading to stroke according to classification of severity by the New York Heart Association classification system (Leveque et al., 2008; Lin and Rugo, 2007; Yamaguchi et al., 2005).

Patients and Method

Study Design and setting

A retrospective longitudinal study of 142 women with non-metastatic BC were included and identified. The patients' demographic, the pathologic tumor features, and molecular subtypes details were recorded.

Women had been diagnosed with BC at clinics of Oncology Teaching Hospital (OTH) and then visited institute for a further follow-up or treatment. All patients who presented from 1 December 2018 to 30 November 2019 who met the study criteria were included.

Data collection and participants

Included demographics, disease stages, co-morbidities, concomitant medications, previous treatments, dose and duration of trastuzumab, frequency of monitoring, symptomatic or asymptomatic cardiac dysfunction, and changes in the treatment. Data were collected with review of medical records and patients files from 2011 to 2019. The following variables were studied: age, TNM staging [stands for tumor (T), nodes (N), and metastases (M)], histopathology, hormone receptor (HR) status, HER2 status, body surface area (BSA), and body mass index (BMI).

HR expression status was examined by IHC, and HER2 protein overexpression and/or gene amplification by IHC.

Inclusion Criteria

1. Female aged 18-years or more.
2. Breast cancer independent of any other primary tumors.
3. All women that enrolled in the study had histological confirmation of breast cancer with HER2 amplification by immunohistochemistry (+3) or FISH study (more than 4 copies) or may be both (if equivocal result by IHC).
4. All women underwent a full cardiac assessment before the initiation of trastuzumab and enrollment in the current study.

Exclusion Criteria

1. Other tumor(s).
2. Male BC.
3. Those with LVEF less than 55%.
4. Severe valvular heart diseases.

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5. Acute myocarditis.
6. Cardiomyopathy.
7. History of heart failure.
8. Pregnancy.
9. Any female in the child bearing age with no contraceptive method.

Trastuzumab

Trastuzumab is a sterile, white to pale yellow, preservative-free lyophilized powder IV infusion. The nominal content of each vial is 440mg trastuzumab, 9.9mg L-histidine HCl, 6.4mg L-histidine, 400mg α, α-trehalose dihydrate, and 1.8mg polysorbate 20, USP. The recommended initial loading dose is 4mg/kg for 90-minute infusion. Trastuzumab is to be diluted in saline.

Cardiac monitoring

In the adjuvant setting perform a serial monitoring of cardiac function at baseline, 3, 6 and 9 months, and then at 12 and 18 months. Monitoring repeated during or following treatment as clinically indicated (Curigliano et al., 2012), and this with level of evidence =1, and grade of recommendation =A.

The adequacy of cardiac monitoring was determined by ECHO cardiograph study at first setting before first dose of trastuzumab 3 months, and 6 months sequel. All echocardiograms were identified in the inpatient files.

In the current study, the standard 8 weeks plus 30 days to allow for flexibility in scheduling and to allow variability in practice and resources across this population was conducted according to current guidelines that recommend baseline evaluation and evaluation every 8 weeks (0, 8, and 16 weeks). Moreover, this study utilized the Cardiac Review and Evaluation Committee definition of cardiac dysfunction, which include at least 1 of the following: (1) cardiomyopathy; (2) HF; (3) S3 gallop, tachycardia, or both; and (4) ↓ LVEF of at least 5% to less than 55% or symptomatic HF, or a decline in LVEF of at least 10% to below 55% or asymptomatic HF (Seidman et al., 2002).

Statistical analysis

A two-sided P value of ≤0.05 was statistically significant for reduction rate of EF%. Mean±SD described for numerical variables. All analyses were conducted by using Statistical Package for Social Sciences version 15.0 for Windows (SPSS Inc., Chicago, Illinois, USA). Analysis of variance (ANOVA) of one way used to determine the differences among trastuzumab doses and cardiac toxicity monitoring by ECHO studies. 3D scatter plot of ECHO1, ECHO2, and ECHO3 as tool for illustrated cardiac monitoring among trastuzumab in BC patients among time of starting adjuvant setting. Odd's ratio used to determine the risk of trastuzumab therapy in relation to study variables on cardiac function.

Results

The mean age of women was 53.54±10.058 years with median of 54.5 years. The mostly distributed age group was belong to fifth decades as 61(43%) patients, followed by 41-50 years 35(24.6%), 61-70 years 24(16.9%), 31-40 years 10(7%), whereas 3(3.2%) females were below age of 30 years, and 6(4.2%) patients over 70 years as shown in table 1.

Concerning body surface area (BSA), table 1 showed that BSA was recorded to 123(86.6%) females with BSA equal or more than 1.65 m^2; while, 19(13.4%) of women were below 1.65 m^2. The mean was 1.81±0.34 m^2 with median of 1.65 m^2.

Regarding BMI of patients, the mean was 30.62±5.51 m^2/kg with median of 30.05 m^2/kg. Most females belonged to overweight and moderate obesity as 44(31%), and 43(30.3%), respectively. While the normal BMI observed in 27(19%) women. The sever obesity presented in 16(11.3%) of patients. The underweight, and morbid obesity presented in 5(3.5%), and 7(4.9%) of patients, respectively as shown in table 1.

Regarding year of BC diagnosis in women, table 2 and figure 1 showed that there were 45(31.7%) of patients diagnosed with early BC in both 2015, and 2016; while, 21(14.8%) of women diagnosed at 2014; and 24(16.9%) of women was diagnosed at 2013.

The most common stage of BC in the study was stage IIIA 33(24.6%) patients, followed by stage IIA 31(23.1%) patients, and stage IIB 30(22.4%) patients; furthermore, the stage IIIC presented in 17(12.7%) of patients; while, stage IA presented in 15(11.2%) of patients; and 4 patients (3%) belonged to stage IIIB. In addition, carcinoma in situ (CIS) presented in 2(1.5%) patients as shown in table 2 and figure 2.

The TNM staging of BC, the T2 stage was common that represented to be 94(70.1%), followed by T1, and T3 as 20(15%), 13(9.7%), respectively; furthermore, 5 patients (3.7%) were belonged to T4, and two patients (1.5%) were T0; additionally, results of table 3-2 showed a high frequency of N0 staging in 49(36.8%), and followed by N1 in 40(30.1%) of patients, N2 in 28(21.1%), and N3 in 16(12%),

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As shown in table 3, the HR (ER and PR) positive was recorded in 75(52.8%) of patients; while, 67(47.2%) patients were HR negative. Moreover, the HER 2neu 2+ was found in 13(9.2%) patients; while, HER 2neu 3+ presented in 129(90.8%) patients; also table 3 showed that the CISH was done for 13(9.3%) of patients.

There were different chemotherapy protocols received by women enrolled in the current study. Table 4 and figure 3 showed that AC chemotherapy was given to 117(82.3%) patients; FEC [5FU, epirubicin, and cyclophosphamide] was given to 5(3.5%); EC [epirubicin and cyclophosphamide] was given to 3(2.1%); and CAF [cyclophosphamide, adriamycin, and fluorouracil] was given to 2(1.4%) patients. Taxane-containing regimen [paclitaxel, or docetaxel] was given to 113(79.5%) patients as 4 cycles (each cycle every 21 days), 11(7.7%) as 3 cycles (each cycle every 21 days), 3(2.1%) as 6 cycles (each cycle every 21 days), and 2(1.4%) as 12 cycles weekly; and TC [docetaxel plus cyclophosphamide] as 4 cycles was given to 3(2.1%) patients.

Moreover, table 3-4 showed that total of 106(74.6%) of women underwent mastectomy; while, the rest 36(25.4%) underwent lumpectomy; furthermore, women received radiotherapy were 81(57.7%); while, 60(42.3%) weren't.

Additionally, hormonal therapy like Aromatase inhibitors received by 20(14.1%) patients; while, 49(34.5%) of women were on tamoxifen. Table 4.

About 131(92.2%) of women in the present study received trastuzumab for one year as 17 doses (one every 21 days for one year duration). While, the rest number of patients were distributed as follow: One woman received 6 doses only; one patient received 10 doses; one reached to 7 doses; one reached to 11 doses; two patients received 8 doses; Another two received trastuzumab as second line; one female received trastuzumab in third and fourth lines as shown in table 5.

Baseline cardiac evaluation was performed in 139(97.8%) of patients by ECHO1; 141(99.3%) had an ECHO2 study within the first 12 weeks of trastuzumab therapy, and 138(97.2%) of patients done ECHO3 study at 24 weeks of therapy. In the entire study, only 97.2% of the patients had cardiac monitoring, was shown in table 6 and figure 3.

Furthermore, at baseline state the ECHO1 study resulted as 123(86.6%) patients were normal (normal readings and findings; LVEF=55-70%); and an abnormal ECHO1 were found as one woman with diastolic dysfunction; one with systolic dysfunction; 4 women with left ventricular hypertrophy; two women with left ventricular dysfunction; one with left atrial dysfunction; 6 patients with hypertensive heart diseases; one woman with mitral valve myxoma. Furthermore, after 12 weeks of trastuzumab therapy, the ECHO2 study was performed; where, normal findings presented in 99(69.7%), eight patients had diastolic dysfunction; 16(11.2%) women with left ventricular hypertrophy; 5(3.5%) women with left ventricular dysfunction; 7(4.9%) patients with hypertensive heart diseases; two women with ischemic heart diseases. In addition, four cases found to having septal wall hypertrophy; mitral valve myxoma; acute coronary syndromes; tricuspid valve dysfunction, one for each. Table 6.

24 weeks after trastuzumab therapy, the ECHO3 study performed; where, 94(66.2%) of patients found to be within normal; two patients still had diastolic dysfunction; 20(14.1%) women found to had left ventricular hypertrophy (16 patients from previous study plus 4 new cases); three patients had left ventricular dysfunction; one woman returned to had left atrial dysfunction; additionally, double number of patients had hypertensive heart diseases (i.e. 7 patient from previous study plus 7 new cases). Finally, four cases found to having same findings from previous ECHO. Table 6

Regarding Ejection fraction (EF), table 7 showed that there were normal EF% that estimated to be 123(86.6%) patients in baseline ECHO1; in 99(69.7%) patients in ECHO2 study; and in 94(66.2%) patients in ECHO3 study with non-significant reduction rate of 20.3%. Normal EF% (>55%) plus abnormal findings presented in 14(9.8%), 30(21.1%), and 27(19%) of patients, which estimated by ECHO1, ECHO2, and ECHO3 studies, respectively, with non-significant reduction rate of 38.5% in EF%. The abnormal EF% (50%) plus abnormal findings noticed in 1(0.7%), 3(2.1%), and 3(2.1%) patients for ECHO studies, accompany with significant reduction rate of 40.9% in the EF% at (p=0.046). Abnormal EF% (<50%; 40%; 30%; <30%) plus abnormal findings were observed 1(0.7%), 9(6.3%), and 14(9.8) of patients, with strongly significant reduction rate 41.7% in EF% at (P<0.000).

Table 8 illustrated that a univariate analysis of Herceptin therapy on baseline characteristics, tumor characteristics and management options as a risk factors for developing cardiac toxicity was shown; where, in age groups 51-60 years [OR=3.35 (95%CI=1.01-5.79)]; 61-70 years [OR=4.37 (95%CI=1.06-2.92)]; and > 70 years [OR=2.382 (95%CI=1.11-4.25)] having high probability (P=0.004; P<0.0001; P=0.05), respectively to develop cardiac toxicity among other groups. Moreover, high BMI represented a strong

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association to make patients treated with trastuzumab for suffering from heart diseases. The overweight [OR=2.178 (95%CI=0.22-6.12)]; moderate obesity [OR=3.91 (95%CI=0.48-6.91)]; sever obesity [OR=3.92 (95%CI=0.76-6.07)] had statistically differences among other groups (P=0.048; P=0.003; P<0.000), respectively.

Furthermore, findings regarding cardiac toxicity and chemotherapy protocols with trastuzumab therapy showed a strong statically association among protocol AC [OR=3.138 (95%CI=0.22-5.94)], (P=0.005). While among taxane [OR=2.555 (95%CI=0.06-4.7)], the association were moderately relative (P=0.056). Table 8.

Additionally, table 8 showed that radiation [OR=2.86 (95%CI=0.19-3.78)] was associated with an increase in the risk of developing cardiac disability (P=0.046).

Regarding BSA, year of diagnosis, BC staging, TNM staging, HR and hormonal therapy, table 8 showed that there were no any contribution between those variables and Herceptin cardiac dysfunction.

Discussion

The findings of the this work regarding age, BSA, BMI, TNM staging of BC, HR, and HER 2neu percentages resemble results of most previous studies conducted in Iraq (Al-Naqqash et al., 2019s; Al-Alwan et al., 2019s, 2018, 2017; Al-Rawaq, 2016; Al-Khafaji, 2010; Al-Naqqash, 2009); where the mean age of women of this study was 53.54±10.058 years, with median of 54.5 years. The mostly distributed age group belonged to the fifth decade as 61(43%) of patients, followed by 41-50 years 35(24.6%). Regard to the BSA, there was recorded 123(86.6%) females equal or more than 1.65 m^2. While 19(13.4%) of women were below 1.65 m^2. The mean BSA was 1.81±0.34 m^2 with median of 1.65 m^2. Regarding the BMI of patients, the mean ±SD was 30.62±5.51 m^2/kg with median of 30.05 m^2/kg. Most of the females belonged to overweight and moderate obesity as 44(31%), and 43(30.3%), respectively. While the normal BMI was observed in 27(19%) women. The most common stage of BC in the study was stage IIIA 33(24.6%) patients, followed by stage IIA 31(23.1%) patients. Stage IIB was 30(22.4%) patients. Regarding TNM staging of BC, the T2 stage was common which is represented to be 94(70.1%). Moreover, the results of table 2 showed a high frequency of N00 staging in 49(36.8. Followed by N1 in 40(30.1%) of patients. The HR (ER and PR) positive was recorded in 75(52.8%) of patients; while, the HER 2neu 2+ was found in 13(9.2%) patients, and HER 2neu 3+ presented in 129(90.8%) patients.

Authors mentioned that age is important factor for the occurrence of BC (Sotiriou et al 2003). In Arabian countries, women were under the age of 50, which is consistence with our findings. Furthermore, in comparative study done among the Iraqi and the British the age was above that showed by our findings; while the US females reported to be in sixth decades of their life (Oussama, 2006).

In a pooled analysis of prospective studies found the risk of BC to be 30% higher in women with a BMI over 31 m^2/kg. This is due to higher estradiol levels associated with increased adipose tissue (Pegram et al., 2012).

The tumor size rank among the strongest predictors of distant metastasis, disease-free, and overall survival, that associate strongly with the presence and number of involved axillary lymph nodes. It is clearly an independent prognostic factor (Fisher et al., 2018; Pegram et al., 2012). The LN status is one of the most important prognostic factors related to the survival and the best predictor of systemic micro-metastases (Fisher et al., 2018; Jabbari et al., 2010).

There were different chemotherapy protocols and anti-cancer agents including surgery types, radiotherapy, hormonal therapy and trastuzumab therapy received by women of the current study. All these treatment options were performed according to the most powerful American and European guidelines like NCCN, ASCO, and ESMO. Thereafter, based on results of several randomized trials, FDA had approved trastuzumab for the adjuvant treatment of HER2 overexpressing BC. Studies of NSABP B-31, NCCTG N9831, HERA, BCIRG 006, and the FinHer study has demonstrated significant benefit in the adjuvant treatment of women with HER2-neu positive BC (Romond et al., 2012). Moreover, Slamon et al., 2006 and Ewer et al., 2005 targeted the using of Adjuvant trastuzumab to reduce BC mortality in Her2-positive early BC patients at the price of some, predominantly reversible, cardiac dysfunction.

Baseline cardiac evaluation was performed in 139(97.8%) of patients by ECHO1; and the second ECHO2 study done for 141(99.3%) had within the first 12 weeks of trastuzumab therapy, and 138(97.2%) of patients done ECHO3 study at 24 weeks of therapy. In this study, the applied guidelines were performed resembling to the ESMO guide 2012. Furthermore, the monitoring for cardiac dysfunction in the adjuvant setting strongly recommended; however, in both early and advanced BC, in addition to the metastatic

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setting, but may be the value of monitoring for cardiotoxicity in a metastatic cancer patient is more likely low. This due to the benefit of the treatment outweighs the cardiac risk (Curigliano et al., 2012).

Different abnormality of ECHO studies and cardiac dysfunctions were demonstrated by the present study during trastuzumab adjuvant setting as diastolic 47 dysfunction; systolic dysfunction (SD); left ventricular hypertrophy (LVH); left ventricular dysfunction (LVD); left atrial dysfunction (LAD); hypertensive heart diseases; mitral valve myxoma; ischemic heart diseases (IHD); septal wall hypertrophy; acute coronary syndromes; tricuspid valve dysfunction, and those finding reflect decline in EF% during the period of trastuzumab administration beside other risk factors such as chemotherapy toxicity especially AC protocol, increasing age of patients, high BMI, positive HER 2nue, as analyzed by the Odds of Logistic regression model. Those results were expected, since almost nearly all trials like the European HERA trial; NSABP B-31; North Central Cancer Treatment Group (NCCTG) N9831; BCIRG 006 demonstrated a different trastuzumab adverse effects, especially adverse effects that is related to cardiac function (Romond et al., 2012). Since 1998, when the FDA approved the use of trastuzumab, the improved outcome associated with such drug was found to be associated with an increased incidence of CHF and asymptomatic reduction in LVEF.

There are several mechanisms have been proposed, such as, the potentiation of prior anthracycline-related cardiac damage; induction of immune-mediated destruction of cardiomyocytes; defects in HER2 signaling required for maintenance of cardiac contractility; an indirect consequence of trastuzumab-related effects outside the heart; decrease in HER2-mediated cardiac survival (Curigliano et al., 2012).

In spite of the improved outcomes associated with the use of trastuzumub, the cardiac toxicity is an apprehension for medical oncologists, cardiologists, and patients. Trastuzumab - induced cardiotoxicity rates are vary. It ranged from 0.8% to 5.1%, and the ↓ LVEF rates ranged from 3.5% to 19% (Romond et al., 2012; Slamon et al., 2011; Tarantini et al., 2012).

It has dragged a huge attention that the cardiac effects of trastuzumab were reported to vary from those of anthracyclines effect; and this has led to the classification of trastuzumab-related chemotherapy-related cardiac dysfunction (CRCD) as Type II (Guarneri et al., 2006; Ewer and Lippman, 2005), as opposed to the irreversible changes associated with anthracyclines (Type I CRCD).

The incidence of serious adverse events during trastuzumab mono-therapy was reported to be low, and the most acute adverse effect is a hypersensitivity-like infusion reaction (Herceptin PI, 2008). When added Herceptin to chemotherapy, CHF was reported in an unexpectedly high number of patients, prompting a detailed retrospective cardiac evaluation (Slamon et al, 2006; Jones et al., 2009).

The concurrent use of trastuzumab with paclitaxel increased CHF percent to 13%. Patients that are receiving concurrent anthracycline and trastuzumab had a 27% incidence of symptomatic heart failure (16% NYHA Grade III/IV) (NCCN, 2018, 2019).

Authors illustrated that trastuzumab in dose-independent manner was associated LVSD appeared to improve with standard medical management including angiotensin converting enzyme inhibitors (NCCN, 2019). Furthermore, data suggested that approximately 80% of the patients may experience symptomatic improvement with standard medical therapy for congestive heart failure (Pegram et al., 2012). In results of this study, there were 17 patients stopped trastuzumab therapy after EF% was dropped below 50%; where, 8(5.6%) women of 17 stopped trastuzumab due to appearance of sever clinical manifestations of cardiac toxicity and the EF% dropped and didn't return to normal level, so the herceptin therapy omitted from their in adjuvant setting. Furthermore, another 9(6.3%) patients completed the therapy to 17 doses after controlling cardiac conditions and returned of EF% to normal level.

Moreover, authors reported that trastuzumab-related cardiac dysfunction does not seem to be dose related and may be responsive to drug withdrawal and/or standard medical therapy, Furthermore, some patients have been reported to have an asymptomatic 20% or greater decrease in LV ejection fraction that spontaneously returned to baseline while continuing on trastuzumab without dose modification or initiation of medical therapy (Pegram et al., 2012) .

The ESMO guidelines identified the risk factors; these include prior treatment with anthracycline chemotherapy, a borderline lower limit of normal LVEF, prior treatment with antihypertensive medication, older age, and a poorly understood result found in 1 trial a BMI >25 kg/m^2 (Curigliano et al., 2012).

Monitoring recommendations are depended on expert opinion and the stringent monitoring used in large clinical trials. The United Kingdom (UK), National Cancer Research Institute recommending baseline and every 4-month cardiac monitoring with either echo or multigated acquisition (MUGA) scan during adjuvant treatment (Jones et al., 2009). The UK guidance on the uses of adjuvant trastuzumab (NICE,

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2006a) is based on the protocol for the European registration trial (HERceptin Adjuvant; HERA) (Smith et al, 2007; Piccart-Gebhart et al, 2005). That trial excluded women with a LVEF of 55% prior to trastuzumab treatment, excluding patients with cardiac comorbidities and 3-monthly LVEF monitoring on therapy (with trastuzumab suspension if LVEF declined) (NICE, 2006).

The modified guidance was published by National Cancer Research Institute in 2009. It has recommended a more proactive approach to monitoring and management of cardiac dysfunction (Jones et al., 2009). Furthermore, Conway et al., in 2010, treated 172 patients with herceptin, 99% had pre-herceptin LVEF measurement but only 74% had a pre-chemotherapy LVEF performed; 4% did not complete trastuzumab due to symptomatic or persistent decline in LVEF. Overall, LVEF declined in 5% of patients; Moreover, appropriate ACEI- initiation and cardiology referral was undertaken in 50% and 71% of cases, respectively. In those with LVEF decline, 60% completed trastuzumab therapy. After NCRI guidance introduction, in 6 months in 2014, 104 patients were commenced on trastuzumab and 98% had pre-chemotherapy LVEF performed, 5% did not complete trastuzumab; 1 due to a decline in LVEF. In all the patients initiated, LVEF declined in 10%; all but one were appropriately commenced on ACEI or referred to cardiology and subsequently 90% of these patients completed trastuzumab. In both cohorts, no patients treated with anthracycline chemotherapy, who had both pre- and post-chemotherapy scans, demonstrated an asymptomatic decline in LVEF. Authors concluded that the introduction of the 2009 NCRI guidelines improved the 52 identification, monitoring and treatment of cardiac dysfunction with a subsequent increase in trastuzumab treatment completion (Conway et al., 2010).

The Canadian Trastuzumab Working Group recommended monitoring at baseline and at 3, 6, 9, and 12 months (Mackey et al., 2008).

Moreover, the ASCO guidelines reflect clinical trial design. Furthermore, LVEF should be further assessed in all patients after completion of chemotherapy and before initiating therapy, and routine LVEF monitoring is recommended at 4 and 8 months. Additionally, further assessment at the end of treatment is recommended for patients requiring CV intervention during treatment. The minimum number of LVEF assessments when following this recommendation is four, compared with five using the NCRI guidelines (Suter et al, 2007); with about a two decade of follow-up involving patients treated in the adjuvant setting with trastuzumab-containing regimens.

Presently, the ASCO and American College of Cardiology are collaborating to develop guidelines for patients undergoing trastuzumab-based therapies, and this effort may provide some clarity; but ideally, guidelines should be evidence based, informed by well-conducted and adequately powered trials, thus conduction of informative studies before establishing arbitrary metrics and labeling them quality indicators were instructed (Dang et al., 2016).

Authors reported that the cardiotoxicity-induced by trastuzumab is reversible, and the early diagnosis is fundamental for providing appropriate medical care. In the joint analysis of the National Surgical Adjuvant Breast and Bowel Project B-31 (NSABP B-31) trial and the North Central Cancer Treatment Group (NCCTG)–N9831 trial, enrolled patients underwent cardiac imaging at baseline, after completion of doxorubicin (usually month 3), and at 6, 9, and 18 months after random assignment (Romond et al., 2012). In the Breast Cancer International Research Group (BCIRG) 006 trial, cardiac imaging was performed seven times during the course of treatment (Nabholtz et al., 2002).

The current study showed that the cardiac monitoring at initial and subsequent during adjuvant trastuzumab therapy in BC patients is an area that requires improvement in Iraq. Actions to increase the rates of cardiac monitoring during this setting are needed, and adequate cardiac monitoring among trastuzumab treated patients should be considered .

Conclusions

Cardiac assessment, and heart function measurement, including EF measurement, performing before chemotherapy is a baseline guide in frequent assessment in the future. Cardiac risk factors management like hypertension before the first cycle of chemotherapy is mandatory. Reassessment of EF after completing chemotherapy and before starting trastuzumab, and repeat measurements throughout therapy is of great value in preventing decline in health status. In the future work, application of specific preventive measurements may be of great benefit in manage anti-cancer agents induce cardiac toxicity. Close follow-up of patients with clinical manifestations of cardiac dysfunction. Apply cardiac monitoring methods in the presenting screening program of breast cancer. Supply each Oncology centers with cardiologic monitoring unite or system. Making a protocol for promoting a multidisciplinary team of oncologists, cardiologists, and approach to the better patient care. More sensitive diagnostic methods are needed to detect early signs

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of myocardial damage like measurement of diastolic function by Doppler echocardiography and noninvasive nuclear imaging techniques as 99mTc-annexin V scintigraphy.

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Table 1. Patients characteristics distribution of the study (n=142).

Characteristics		No.(%)	Mean±SD
Age (years)	20-30	3 (2.1)	53.54±10.058
	31-40	10 (7)	
	41-50	35 (24.6)	
	51-60	61 (43)	
	61-70	24 (16.9)	
	>70	6 (4.2)	
	Total	142	
Body surface area (BSA) (m^2)	<1.65	19 (13.4)	1.81±0.34
	≥1.65	123 (86.6)	
	Total	142	
Body mass index BMI (m^2/Kg)	Underweight (<18.5)	5 (3.5)	30.62±5.51
	Normal (18.6-24.9)	27 (19)	
	Overweight (25-29.9)	44 (31)	
	Moderate obesity (30-34.9)	43 (30.3)	
	Sever obesity (35-39.9)	16 (11.3)	
	Morbid obesity (>40)	7 (4.9)	
	Total	142	

Table 2. Breast cancer characteristics distribution of the study (n=142).

Characteristics		No. (%)
Year of diagnosis	2011	1 (0.7)
	2012	6 (4.2)
	2013	24 (16.9)
	2014	21 (14.8)
	2015	45 (31.7)
	2016	45 (31.7)
Staging	Carcinoma in situ (CIS)	2 (1.5)
	IA	15 (11.2)
	IIA	31 (23.1)
	IIB	30 (22.7)
	IIIA	33 (24.6)
	IIIB	4 (3)
	IIIC	17 (12.7)
	Total	132
Tumor sizes (mm)	≤20	19 (14.2)
	20-50	75 (56)
	>50	7 (5.2)
	Tx	33 (24.6)
	Total	134
T staging	T0	2 (1.5)
	T1	20 (15)
	T2	94 (70.1)
	T3	13 (9.7)
	T4	5 (3.7)
	Total	134
N staging	N0	49 (36.8)
	N1	40 (30.1)
	N2	28 (21.1)
	N3	16 (12)
	Total	133

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Table 3. Breast cancer HR and HER 2neu characteristic of the study (n=142).

Characteristics		No. (%)
Hormone receptor (HR)	Positive	75 (52.8)
	Negative	67 (47.2)
	Total	142
HER 2	2+	13 (9.2)
	3+	129 (90.8)
	Total	142
Chromogenic in situ hybridization (CISH)	Done	13 (9.3)
	Not	127 (90.7)
	Total	140

Table 4: Breast cancer management of the study (n=142).

Management			No. (%)
Chemotherapy protocols (n=142)	Adriamycin and cyclophosphamide AC*		117 (82.3)
	5FU, epirubicin and cyclophosphamide (3 cycles) FEC		5 (3.5)
	Epirubicin and cyclophosphamide (4 cycles) EC		3 (2.1)
	Cyclophosphamide, Adriamycin, and fluorouracil (6 cycles) CAF		2 (1.4)
	Taxane** T	12 cycles weekly	2 (1.4)
		3 cycles	11 (7.7)
		4 cycles	113 (79.5)
		6 cycles	3 (2.1)
	Docetaxel and cyclophosphamide (4 cycles) TC		3 (2.1)
Surgery types	BCS		36 (25.4)
	Mastectomy		106 (74.6)
Radiotherapy	Received		81 (57.7)
	Not		60 (42.3)
Hormonal	Aromatase inhibitors		20 (14.1)
	Tamoxifen		49 (34.5)
*AC protocols used as 3 cycles in 8 patients. **Taxane protocols recorded in the study.			

Table 5: Trastuzumab doses distribution of the study.

Trastuzumab doses	No. (%)
6	1 (0.7)
7	1 (0.7)
8	2 (1.4)
10	1(0.7)
11	1 (0.7)
17	131 (92.2)
20	1 (0.7)
6 or 10 +second line (2 month events)	2 (1.4)
17+third line	1 (0.7)
17+fourth line	1 (0.7)

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Table 6. ANOVA (one way) analysis for cardiac monitoring by ECHO1, ECHO2, and ECHO3 among breast cancer (BC) patients received trastuzumab therapy (n=142).

Characteristics	ECHO 1	ECHO 2	ECHO 3	ANOVA (one way)	df	P value
	No. (%)					
Normal	123 (86.6)	99 (69.7)	94 (66.2)	6.4	14	0.012
Diastolic dysfunction (DD)	1 (0.7)	8 (5.6)	2 (1.4)			
Systolic dysfunction	1 (0.7)	0	0			
Left ventricular hypertrophy (LVH)	4 (2.8)	16 (11.2)	20 (14.1)			
Left ventricular dysfunction (LVD)	2 (1.4)	5 (3.5)	3 (2.1)			
Left atrial dysfunction (LAD)	1 (0.7)	0	1 (0.7)			
Hypertensive heart diseases (HHD)	6 (4.2)	7 (4.9)	14 (9.9)			
Ischemic heart diseases	0	2 (1.4)	0			
Other *	1 (0.7)	4 (2.8)	4 (2.8)			
Not done	3 (2.1)	1 (0.7)	4 (2.8)			
Other *: Septal wall hypertrophy; Mitral valve myxoma; Acute coronary syndromes; Tricuspid valve dysfunction						

Table 7. Percent (%) of Ejection fraction (EF) reduction rates during cardiac monitoring by ECHO studies.

Characteristics	ECHO 1	ECHO 2	ECHO 3	Ejection fraction reduction rate (%)	P value
	No. (%)				
Normal EF% (55-70%) + normal findings	123 (86.6)	99 (69.7)	94 (66.2)	20.3	0.09
Normal EF% (>55%) + abnormal findings	14 (9.8)	30 (21.1)	27 (19)	38.5	0.054
Abnormal EF% (50%) + Abnormal findings	1 (0.7)	3 (2.1)	3 (2.1)*	40.9	0.046
Abnormal EF% (<50%; 40%; 30%; <30%) + Abnormal findings	1 (0.7)	9 (6.3)	14 (9.8)*	41.7	<0.000
Not done	3 (2.1)	1 (0.7)	4 (2.8)		
*As mentioned in trastuzumab therapy, 8(5.6%) women stopped trastuzumab due to appearance of sever clinical manifestations of cardiac toxicity and the EF% dropped and didn't return to normal level, so the Herceptin therapy omitted for their in adjuvant setting. Another groups of 9(6.3%) patients, who had decreasing in the EF% during the course of trastuzumab doses, they completed their therapy to 17 doses after controlling cardiac conditions and returned of EF% to normal level.					

Table 8. Logistic regression model evaluating the Odds of cardiac monitoring among patients with BC treated with adjuvant trastuzumab

Variables		Herceptin therapy OR (95% CI)	P value
Age (years)	20-30	1.214 (0.27-2.33)	0.5
	31-40	1.2 (0.3-4.79)	0.22
	41-50	0.988 (0.9-1.08)	0.09
	51-60	3.35 (1.01-5.79)	0.004
	61-70	4.37 (1.06-2.92)	<0.001
	>70	2.382 (1.11-4.25)	0.05
BSA (m^2)	<1.65	0.76 (0.55-1.15)	0.72
	≥1.65	0.94 (0.65-1.35)	0.8
BMI (m^2/Kg)	Underweight (<18.5)	0.92 (0.74-1.14)	0.99
	Normal (18.6-24.9)	1 (0.79-1.46)	0.083
	Overweight (25-29.9)	2.178 (0.22-6.12)	0.048
	Moderate obesity (30-34.9)	3.91 (0.48-6.91)	0.003
	Sever obesity (35-39.9)	3.92 (0.76-6.07)	<0.000
	Morbid obesity (>40)	2.991 (0.91-4.09)	0.059
Year of diagnosis	2011	1.13 (0.87-1.5)	0.08
	2012	1.39 (1.01-1.7)	0.15
	2013	1.44 (1.11- 2.66)	0.27
	2014	0.96 (0.72-1.16)	0.88
	2015	1.5 (0.69-4.44)	0.9
	2016	0.54 (0.3-0.97)	0.1
Staging	Carcinoma in situ	0.87 (0.21-3.5)	0.25
	IA	1.4 (0.32-6.11)	0.34
	IIA	1.06 (1-1.129)	0.09
	IIB	1.02 (.88-1.17)	0.72
	IIIA	1.31 (0.73-2.35)	0.06
	IIIB	1.2 (0.94-1.52)	0.98
	IIIC	1.83 (1.53-2.44)	0.7
T staging	T0	0.81 (0.08-7.36)	0.38
	T1	1.01 (0.89-1.13)	0.99
	T2	1.37 (0.34-5.5)	0.67
	T3	0.98 (0.9-1.06)	0.083
	T4	1.39 (0.33-5.61)	0.76
N staging	N0	0.28 (0.05-1.58)	0.6
	N1	0.32 (0.07-1.43)	0.55
	N2	1.12 (0.88-1.42)	0.095
	N3	0.65 (0.07-6.01)	0.75
HR	Positive	1.024 (0.94-1.11)	0.45
	Negative	0.675 (0.17-2.7)	0.99
Chemotherapy	AC	3.138 (0.22-5.94)	0.005
	Taxane	2.555 (0.06-4.7)	0.056
Surgery	BCS	2.436 (0.08-2.35)	0.057
	Mastectomy	2.4 (0.77-3.05)	0.053
Radiotherapy		0.86 (0.19-3.78)	0.046
Hormonal therapy	Aromatase inhibitors	1.27 (1.11-4.33)	0.6
	Tamoxifen	0.913 (0.85-0.97)	0.91

BSA, body surface area; BMI, body mass index; T, tumor size; N, lymph node; HR, hormonal receptor; AC, Adriamycin and cyclophosphamide; BCS, breast conservative surgery

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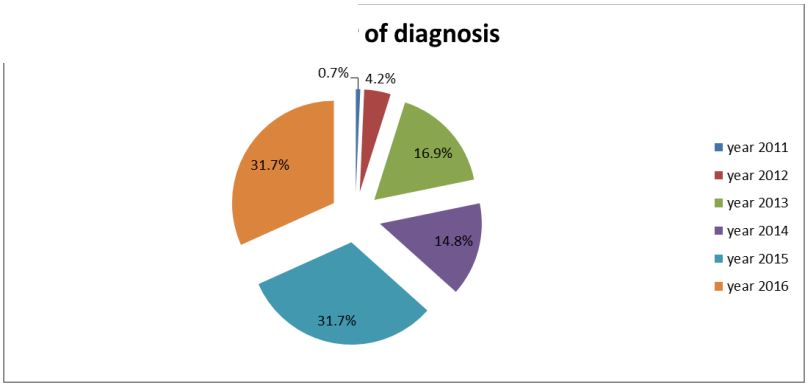

Figure 2. Bar chart of breast cancer (BC) staging of the study.

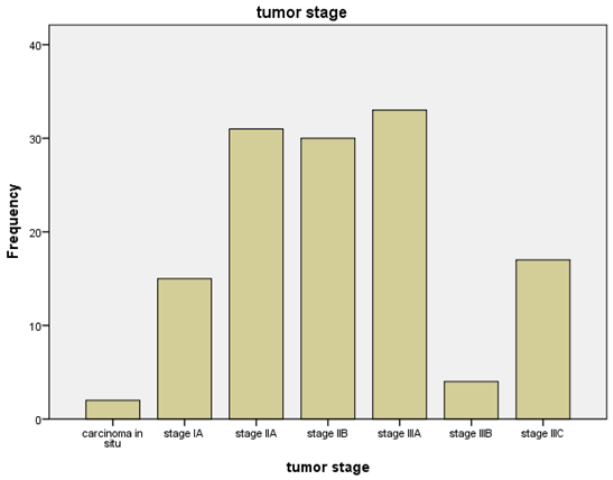

Figure 3. Bar chart of cardiac monitoring by ECHO1, ECHO2, and ECHO3 among BC patients received Herceptin therapy