International Journal of Chemical and Biochemical Sciences
(ISSN 2226-9614)

Journal Home page: www.iscientific.org/Journal.html

Radioisotope Scan (^{99m}TC Sestamibi Myocardial perfusion Scintigraphy) for Assessment of Cardiac Toxicity of Adjuvant Trastuzumab and Paclitaxel in HER -2 +ve Breast Cancer

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Abstract

ERBB2 oncogenes, found in 20-25% of breast cancer cases, cause aggressive disease. Trastuzumab may cause cardiotoxicity yet improves disease outcome by targeting HER2. Trastuzumab and chemotherapy are used in treatment plan for HER2-positive breast cancer. To evaluate Cardiac toxicity of concurrent Trustuzumab and Paclitaxel in Adjuvant treatment of HER-2 positive Breast Cancer using Radioisotope Scan. This was prospective hospital-based study at Qena University Hospital, with 30 participants post-radical surgery and anthracycline-based chemotherapy for unilateral ductal carcinoma, HER2-positive. Physical exams, lab tests, ECG, Echocardiography, and cardiac scan were done. Adjuvant trastuzumab administered with paclitaxel for 4 cycles, then continued for 1 year. Other risk factors for cardiovascular disease in the studied patients included: Age >55 (50%), obesity (43.3%), hypertension, hyperlipidemia (30%), diabetes (16.7%). 30% showed <5% reduction in EF% after 4 cycles of trastuzumab and Paclitaxel adjuvant treatment while 60% had <5% EF% reduction, 16.7% had 5-10% EF% reduction, 20% had 10-15% EF% reduction, and 3.3% had >15% EF% reduction after 12 month of trastuzumab alone, this difference was statistically significant. There was statistically insignificant difference in Cardiac muscle perfusion impairment either after 12 months trastuzumab alone, 4 cycles trastuzumab and Paclitaxel adjuvant treatment and at baseline. We revealed that regarding LVEF%, there was statistically significant impairment after 12 months of trastuzumab alone than those who received trastuzumab and Paclitaxel adjuvant treatment. However, cardiac scan did not differ significantly.

Keywords: Myocardial perfusion scintigraphy, 99mTC Sesta mibi ,Trastuzumab, Paclitaxel, HER-2 Positive, Breast Cancer.

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1. Introduction

With an annual incidence of over 10% of new cancer diagnoses, breast cancer is the most common form of cancer among women in the United States. It also ranks as the second highest cause of cancer-related mortality in women worldwide [1, 2]. The ERBB2 oncogene, also known as HER2 or HER2/neu, is amplified or overexpressed in about 20-25% of initial invasive breast cancers. This is associated with a more aggressive progression of the disease and worse overall survival rates [3]. The approval of treatments specifically targeting HER2 has led to considerable improvement in outcomes for patients diagnosed with all

stages of HER2-positive breast cancer [4]. The current approach to treating HER2-positive breast cancer comprises a combination of chemotherapy and targeted therapy that specifically targets the HER2 protein. One commonly used and successful treatment regimen is the combination of albumin-paclitaxel and Trastuzumab [5]. Trastuzumab, a monoclonal antibody that has been humanized to target the extracellular domain of HER2, has shown improved disease-free and overall survival rates. Nevertheless, it is linked to cardiotoxicity, resulting in either a gradual decrease in left ventricular ejection fraction without symptoms or the development of symptomatic heart failure [6]. The cause of trastuzumab-induced left ventricular systolic dysfunction is associated with the inhibition of HER2 signaling, which disrupts the usual stress response and cellular repair processes of heart muscle cells [7]. Trastuzumab has modest effectiveness when used alone, but it showed significant effectiveness when used in combination with chemotherapy as a neoadjuvant, adjuvant and metastatic treatment in HER-2/neu positive breast cancer [8,9]. The main aim of this study was to evaluate Cardiac toxicity of concurrent Trustuzumab and Paclitaxel in Adjuvant treatment of HER-2 positive Breast Cancer using Radioisotope Scan.

2. Patients and Methods

This investigation is characterized as a prospective hospital-based study conducted at the Clinical Oncology Department of Qena University Hospital in Qena, Egypt. The study population consists of thirty individuals who have undergone radical surgery and received anthracycline-based chemotherapy, are over 30 years old, and have histologically confirmed unilateral ductal carcinoma of the breast without indications of distant metastasis or concurrent malignancies. Additionally, participants must exhibit normal cardiac, renal, and pulmonary functions.

2.1. Inclusion Criteria

- Age (25-65) years.
- Pathology proven breast cancer with positive her 2 neu receptor.

2.2. Exclusion Criteria

- Age <25 and >65 years.
- Pathology proven breast cancer with negative her 2 neu receptor.
- Cardiac patient.
- Not pathology proven breast cancer.

3. Methods

The methodology entailed a comprehensive evaluation of patients, which included collecting data on personal background (such as demographics and habits, particularly smoking), reproductive history (including menstrual details, pregnancies, and hormonal therapies), drug sensitivity, and medical history (including cardiac, hypertension, chest, renal, liver, and blood diseases). Thorough documenting of breast symptoms, previous operations, and family history, particularly cases of breast or ovarian cancer in close relatives, was crucial for the inquiry, along with careful evaluation of other types of cancer within the family. The process of patient characterization included documenting the age and sex of the patients, as well as the size of the tumor, histological characteristics, and the status of K167 and hormone receptors. The physical examinations included several subjects. The patient overall condition was evaluated for signs of discomfort, cachexia, or pallor. Additionally, the symmetry of the breasts, any changes in the skin such as redness, dimpling, or swelling, any changes in the nipples such as inversion or discharge, and any changes in the areola were examined. During palpation, anomalies in the breast tissue were detected, along with enlargement or discomfort in the axillary, supraclavicular, and infraclavicular lymph nodes, lumps in the chest wall, and inversion or discharge of the nipple. Indications of underlying issues may include alterations in the skin and tissue, such as dimpling or puckering (also known as peau d'orange), as well as redness or edema. Noticeable enlargement of axillary lymph nodes may indicate the spread of malignancy to the lymph nodes. Standard laboratory testing included a comprehensive blood analysis (CBC), Renal function and Liver function. Transthoracic echocardiography (TTE) was conducted at the beginning, every three months, and at the end of one year of trustuzumab therapy to evaluate heart function. The echocardiographic assessments were performed using a commercially accessible echocardiography machine in the cardiology department, using a 1.5–3.6 MHz multi-frequency phased array probe. For the echocardiographic assessment, the research participants were positioned lying on their backs, and the assessments were conducted using the long axis left parasternal and apical windows. The measurements were performed following the criteria established by the American Society of Echocardiography (ASE). The evaluation included calculating the left ventricular ejection fraction (EF%) by using M-mode and the Modified Simpson technique. M-mode and two-dimensional (2D) echocardiography were used to determine the ejection fraction (EF%) (Figure 1). The diagnostic criteria for left ventricular systolic dysfunction was established as a left ventricular ejection fraction (LVEF) of less than 54% in females. The treatment plan includes providing adjuvant trastuzumab therapy with 4 cycles of paclitaxel, followed by a total duration of 1 year of trastuzumab therapy. Patients performed certain procedures as part of the cardiac evaluation before and after trustuzumab therapy. At first, patients were given adjuvant trustuzumab treatment, which included receiving 4 cycles of pactlitaxel therapy followed by a continuation of trustuzumab therapy for a total of 1 year. During the therapy, patients were regularly assessed using echocardiography. The assessments were place at the beginning of the treatment, every three months afterward, and at the end of the one-year trustuzumab regimen. In addition, patients had pre- and post-treatment cardiac scans to evaluate functional cardiac damage.

3.1. 99m Tc-SestaMIBI rest myocardial perfusion gated SPECT

Images were taken about 60 minutes after injection of 660 MBq of the tracer. Rest images were acquired in GATED SPECT mode and were constructed in short, horizontal, and vertical long axis views to generate tomographic slices. After completion, the procedure, varying from 1-2 hours, allowed individuals to resume normal activities. The radiotracer naturally exited the body through urine in a few days. The compilation of individual patient data was acquired from hospital records, therefore contributing to

a thorough assessment of the efficacy and safety profile of trustuzumab treatment.

3.2. Statistical analysis

IBM SPSS version 22.0 was used to analyses computer-generated data. To express quantitative data, percentages and numbers were employed. Chi-Square adjustment was applied to tables demonstrating non continuous data and t.test for continuous data.

3. Results

This research included a cohort of 30 individuals who had adjuvant therapy for HER-2 positive breast cancer, receiving trastuzumab and Paclitaxel. The age of the participants varied from 43 to 61 years, with a mean age of 54.4±4.89. The tumor size varied from 2.8 to 5.9 cm, with a mean value of 4.16±0.84. 80% of the cases were diagnosed as invasive ductal carcinoma, while the remaining 20% were classified as invasive lobular carcinoma. 53.3% of the tumors were located on the right side. Estrogen receptor was discovered in 66.7% of patients, whereas Progesterone receptor was detected in 60% of patients. The Ki67 level varied from 7 to 34, with a mean value of 14.6±9.01. Among the participants who participated, 50% were over the age of 55, 43.3% were obese, and 30% had both hypertension and hyperlipidemia. Additionally, 16.7% had diabetes mellitus. Among our included subjects, 30% showed <5% reduction in EF% and no case showed higher reduction after 4 cycles of trastuzumab and Paclitaxel adjuvant treatment while 60% had <5% EF% reduction, 16.7% had 5-10% EF% reduction, 20% had 10-15% EF% reduction, and 3.3% had >15% EF% reduction after 12 month of trastuzumab alone, this difference was statistically significant. LVEF% ranged between 1.45-15.38% with mean value of 5.34±5.07 after 12 month of trastuzumab alone that was statistically significant higher than those who received trastuzumab and Paclitaxel adjuvant treatment. There was statistically insignificant difference in Cardiac muscle perfusion impairment either after 12 months trastuzumab alone, 4 cycles trastuzumab and Paclitaxel adjuvant treatment and at baseline (Table 1).

4. Discussion

The scope of our study included individuals between the ages of 43 and 61, with an average age of 54.4±4.89. The size of the tumors seen varied between 2.8 and 5.9 cm, with an average diameter of 4.16±0.84. The majority of cases were characterized by invasive ductal carcinoma (80%), followed by lobular carcinoma (20%). Additionally, right-sided tumors were the most prevalent, accounting for 53.3% of cases. Estrogen receptors were detected in 66.7% of cases, progesterone receptors in 60% of cases, and Ki67 levels ranged from 7 to 34 (with a mean of 14.6±9.01). Hussain Y et al. [10] conducted an investigation to assess the cardiac safety of trastuzumab in patients with HER2-positive breast cancer, which supports our own research results. The median age of the group was 54, with a range of 47 to 60. The majority of cases of breast cancer are invasive ductal carcinoma (95%), whereas invasive lobular carcinoma accounts for a smaller percentage (5%). The patients exhibited 47% progesterone receptors and 58% estrogen receptors. Debien V, et al. [11] conducted a study to evaluate the effectiveness of adjuvant paclitaxel and trastuzumab in patients from Belgium and Italy who had HER2-positive breast cancer with tumors measuring between 0.5 and 2 cm and no involvement of nearby lymph nodes. The median age was 59.5 years. The tumors were of varying sizes, ranging from 0.5 to 2 centimeters in diameter. 4. The most common types of carcinomas were invasive ductal (86.3%) and lobular (7.8%) carcinomas. The patients exhibited progesterone receptors in 68.7% of cases and estrogen receptors in 85% of cases. Half of our patients were aged 55 or older, 43.3% were obese, 30% had both hypertension and hyperlipidemia, and 16.7% had diabetes mellitus. We endorse the investigation conducted by Yu AF, et al. [12] on the cardiac safety of paclitaxel in combination with trastuzumab and pertuzumab for patients with HER2-positive metastatic breast cancer. Out of the total of 42 patients, which accounts for 61% of the sample, 19 patients (28%) had hypertension, 8 patients (12%) had diabetes, 11 patients (16%) had hyperlipidemia, and 26 patients (38%) had a history of smoking. Echocardiographic parameters were unchanged between trastuzumab and Paclitaxel adjuvant therapy for HER-2 positive breast cancer and baseline. Trastuzumab monotherapy significantly reduced left ventricular ejection fraction (LVEF%). In a study conducted by Dang C, et al. [13], it was discovered that 10% of the patients had baseline left ventricular ejection fraction (LVEF) values ranging from 50% to 55%, whereas 90% of the people had LVEF values over 55%. The majority of patients saw LVEF reductions of less than 10% at different time intervals (84% at 12 weeks, 80% at 6 months, and 74% at 1 year). A small percentage of patients observed drops ranging from 10% to 15% (7%, 9%, and 9% at 1 year), while an even smaller percentage experienced reductions greater than 16% (<1%, 1%, and 2% at 1 year) (Table 2). Piotrowski G, et al. [14] conducted echocardiography at 3 months, 6 months, and 9 months. They discovered that out of the patients examined, 52 individuals (20.55%) had asymptomatic left ventricular dysfunction (43), symptomatic heart failure (6), new asymptomatic left bundle branch block (1), and new negative T-waves in electrocardiogram (2). Treatment decreased left ventricular ejection fraction (LVEF). An substantial reduction in left ventricular ejection fraction (LVEF) was observed, with statistical significance ($p < 0.05$). Our study revealed that 30% of participants saw a drop in EF% of less than 5% after undergoing 4 cycles of trastuzumab plus Paclitaxel adjuvant therapy. In contrast, after 12 months of trastuzumabT treatment, 60% had a decrease of less than 5%, 16.7% had a decrease of 5-10%, 20% had a decrease of 10-15%, and 3.3% had a decrease of more than 15%. Significant disparity with statistical significance. The left ventricular ejection fraction (LVEF%) varied between 1.45% and 15.38%, with an average of 5.34±5.07% after 12 months of receiving just trastuzumab. This average was substantially greater than the LVEF% of individuals who had both trastuzumab and Paclitaxel adjuvant, as reported by Schneider BP, et al. [15] assessed the safety of paclitaxel-trastuzumab adjuvant treatment for early-stage breast cancer, specifically focusing on congestive heart failure (CHF) and left ventricular ejection fraction (LVEF). The results of our investigation align. Trastuzumab as a standalone therapy had a more pronounced effect in reducing left ventricular ejection fraction (LVEF) compared to the use of Paclitaxel as an additional treatment. Huang L. et al. [16] conducted a comparison of the effectiveness and safety of neoadjuvant treatment with epirubicin (E) and carboplatin (C) vs paclitaxel (P) and trastuzumab (H).

Table 1: Participating subjects Characteristics

		N=30
Age (year)	Range (median)	43-61 (54.5)
	Mean ± SD	54.4±4.89
Tumor size	Range (median)	2.8-5.9 (3.9)
	Mean ± SD	4.16±0.84
Side	Right breast	16 (53.3%)
	Left breast	14 (46.7%)
Histopathology	invasive ductal carcinoma	24 (80%)
	invasive lobular carcinoma	6 (20%)
Stage	1A	11 (36.7%)
	2A	10 (33.3%)
	2B	6 (20%)
	3A	3 (10%)
Estrogen receptor	Yes	20 (66.7%)
	NO	10 (33.3%)
Progesterone receptor	Yes	18 (60%)
	No	12 (40%)
Ki67	Range (median)	7-34 (10)
	Mean ± SD	14.6±9.01
Other risk factors for cardiovascular diseases		
Age >55year	15	50%
Obesity	13	43.3%
HTN	9	30%
Hyperlipidemia	9	30%
DM	5	16.7%

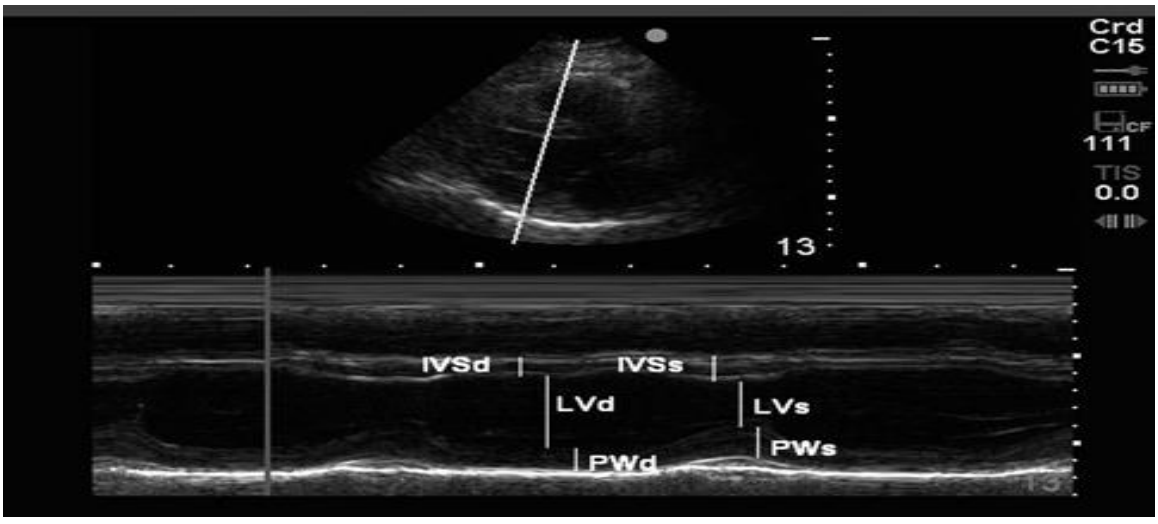

Figure 1: Measurement of EF by M-Mode

Table 2: EF% reduction rate after 4 cycles of trastuzumab and Paclitaxel adjuvant ttt and after 12 month of trastuzumab alone

		after 4 cycles of trastuzumab and Paclitaxel adjuvant ttt N=30		after 12 month of trastuzumab alone N=30		Test of sig
		N	%			P-value
LVEF% reduction	<5%	9	30%	18	60%	0.0001
	5-10%	0	0%	5	16.7%	
	10-15%	0	0%	6	20%	
	>15%	0	0%	1	3.3%	
LVEF% reduction	Range (median)	0-3 (0)		1.45-15.38 (1.8)		0.0001
	Mean ± SD	0.55±0.97		5.34±5.07		

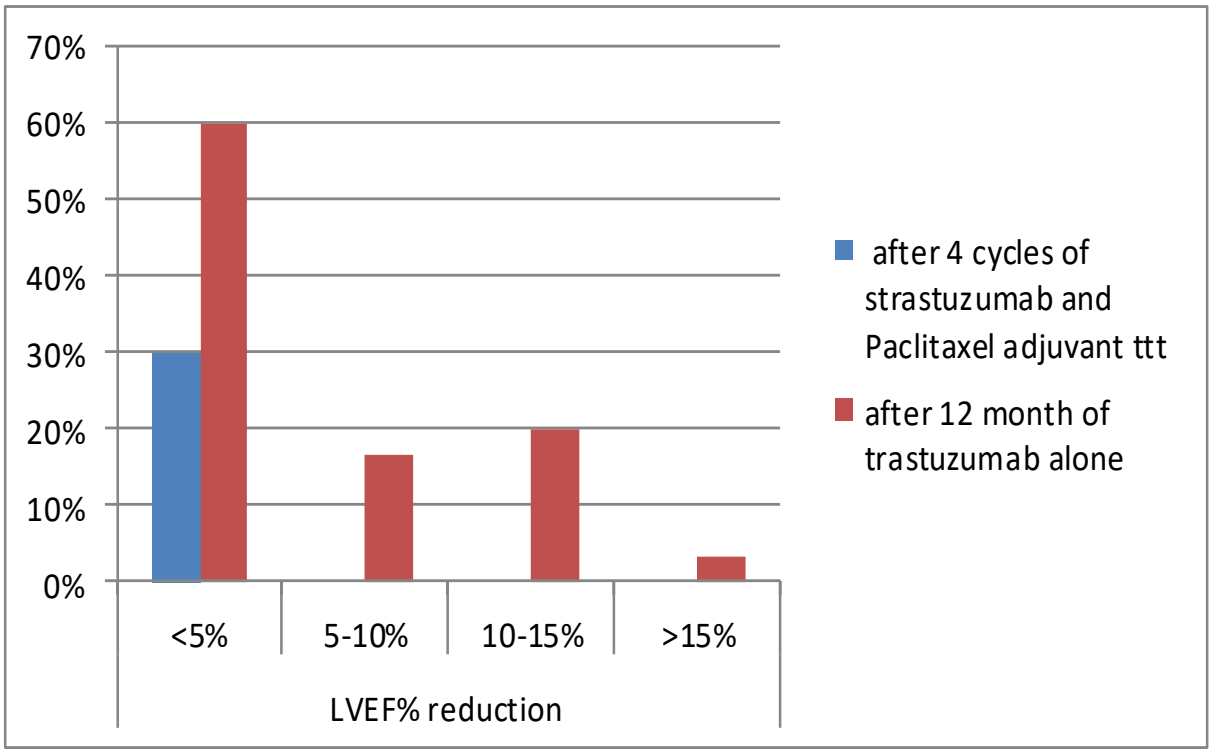

Figure 2: LVEF% reduction distribution of the studied population

Table 3: Comparison of cardiac muscle perfusion before and after intervention in participating subjects

		Baseline		After 4 cycles trastuzumab and Paclitaxel adjuvant ttt		After 12 months trastuzumab alone		Baseline vs after adjuventtrastuzumab& Paclitaxel	Baseline vs trastuzumab alone
		N=30		*N=30*		*N=30*			
		N	%	N	%	N	N	***P-value***	P-value
cardiac muscle perfusion	impaired	1	3.3%	2	6.7%	2	6.7%	0.424	0.809
	Normal	29	96.7%	28	93.3%	28	93.3%		

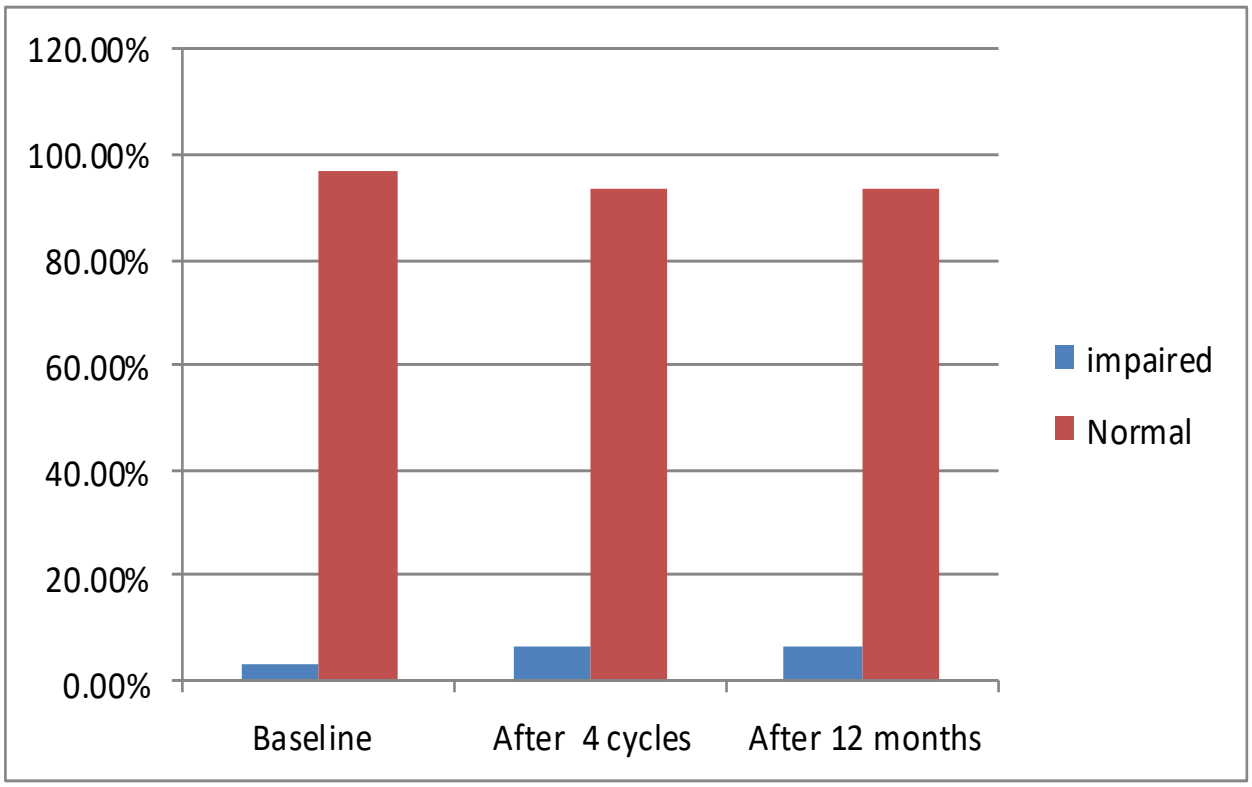

Figure 3: Impaired cardiac muscle perfusion in participating subjects

Left ventricular ejection fraction (LVEF) measurements before and after 2 and 4 neoadjuvant rounds. The subjects from both groups had normal left ventricular ejection fraction (LVEF) throughout the duration of the research. Following 2 cycles, 5 patients with pulmonary capillary hemangiomatosis (PCH) had left ventricular ejection fraction (LVEF) reductions above 10%, which accounted for 11.9% of the patients. Additionally, 3 patients (7.3%) encountered similar LVEF declines after 4 cycles (Figure 2). In accordance with Yu AF, et al. [12], it is confirmed that none of the patients had left ventricular systolic dysfunction (grades 3 or 4) after undergoing baseline and every fourth cycle (every 3 months) echocardiographic left ventricular ejection fraction (LVEF) assessments. The initial average left ventricular ejection fraction (LVEF) was 64%, with a range of 50% to 72%, and remained consistent throughout the duration of the trial. The individual with asymptomatic grade 2 left ventricular ejection fraction saw a decrease of 3.0% in their LVEF. One patient saw a decrease of 16% in left ventricular ejection fraction (LVEF), going from 72% at the beginning to 55% after 15 months. Another patient had a larger decrease of 50% (from 10%–15% at

baseline to 47% after 9 months). Barroso-Sousa R, et al. [17] shown a substantial reduction in asymptomatic left ventricular ejection fraction (LVEF) with the use of adjuvant trastuzumab emtansine (Figure 3). There was no statistically significant variation in cardiac muscle perfusion deficit after 12 months of trastuzumab alone, 4 cycles with Paclitaxel adjuvant treatment, or at the beginning of the study. Jaques R, et al. [18] assessed the efficacy of Trastuzumab in treating breast cancer that is positive for the HER2 protein. There was a substantial rise in the number of individuals with cardiac dysfunction, namely those with impaired muscle perfusion (Table 3).

5. Conclusion

In the current study, we evaluated cardiac toxicity of concurrent administration of Trastuzumab plus Paclitaxel in post operative treatment of HER-2 +ve Breast cancer. We revealed that regarding LVEF%, there was statistically significant higher after 12 months of trastuzumab alone than those who received trastuzumab and Paclitaxel adjuvant treatment. However, cardiac scan did not differ significantly.

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