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A RETROSPECTIVE ANALYSIS OF CARDIOTOXICITY WITH DOXORUBICIN AND TRASTUZUMAB IN BREAST CANCER HER-2 POSITIVE PATIENTS

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ABSTRACT

Background: Breast cancer is the most prevalent cause of mortality for women worldwide, and its prevalence is rising in emerging countries. The widespread availability of numerous drugs that target the HER2 receptor has led to improvements in survival rates for patients with Human Epidermal Growth Factor Receptor-2-positive (HER2+) breast cancer over the past few decades.
Aim: To study the cardiotoxicity associated with the use of doxorubicin and trastuzumab in HER-2 positive breast cancer patients, a retrospective analysis.
Methodology: A retrospective analysis, Patients were screened based on inclusion and exclusion criteria. The self-designed and validated questionnaire was used to assess the cardiotoxicity with doxorubicin and trastuzumab in breast cancer HER-2 positive patients. Collected data was tabulated and interpreted using statistical software.
Results: Upon reviewing demographic data from 117 subjects, it was noted that breast cancer is most prevalent among individuals over 65 years old, with 51 (40.51%) subjects, significant at p=0.03436. All subjects in the study were female except one male. A higher proportion of subjects with a BMI of 30-34 kg/m2 were reported, with 53 (45.20%) subjects, significant at p=0.04131. Among social habits, regular smokers were found to be at a higher risk of breast cancer, significant at p=0.02115. Late menopause was associated with increased risk, with 54 (48%) subjects, significant at p=0.03887. The assessment of cardiotoxicity with doxorubicin pre- and post-therapy using ejection fraction (EF) was statistically analyzed with a p-value of 0.000017. Trastuzumab at a dose of 2mg/kg showed an EF assessment of 0.2035, statistically insignificant for cardiotoxicity. However, at a dose of 8mg/kg, trastuzumab showed a statistically significant EF assessment of 0.000018.
Conclusion: This study found that breast cancer is common among older individuals, those with higher BMI, lower socioeconomic status, service workers, late menopause, and regular tobacco users. Trastuzumab at 2mg/kg showed no cardiotoxicity, while both trastuzumab at 8mg/kg and doxorubicin exhibited similar cardiotoxicity effects, with more deaths associated with doxorubicin. Therefore, trastuzumab at a lower dose appears to be effective and safe.

INTRODUCTION

Breast cancer occurs when aberrant breast cells develop into tumors. If left untreated, tumors may migrate throughout the body and be dangerous. Breast cancer cells arise in the breast's milk ducts and lactate-producing lobules [1]. Cancerous cells can migrate into surrounding breast tissue, known as invasion

[2]. This produces tumors, which cause lumps or thickening.[1]. Cardiotoxicity is an inclusive term that alludes to toxicity that can impact the heart in two ways: directly, by destroying the heart structure, and indirectly, by causing thrombotic states and hemodynamic changes in blood flow [2]. Female breast cancer now ranks as the most prevalent cancer diagnosed worldwide outnumbering lung cancer [3]. In 2023, 297,790 women in the United States are expected to be diagnosed with invasive breast cancer, while 55,720 will be diagnosed with non-invasive breast cancer (in situ) [4].

Human Epidermal Growth Factor Receptor 2 (HER2) positive breast cancer is a subtype associated with aggressive illness and a poor prognosis [5]. The treatment paradigm for HER-2 positive breast cancer frequently combines chemotherapy and targeted therapy with trastuzumab all of which have dramatically improved results. However, these therapy options are not without danger. Doxorubicin, a regularly used chemotherapeutic medication, is renowned for its cardiotoxic effects, which can cause left ventricular dysfunction or heart failure [6]. The treatment paradigm for HER-2 positive breast cancer frequently combines chemotherapy and targeted therapy with trastuzumab all of which have dramatically improved results. However, these therapy options are not without danger. Doxorubicin, a regularly used chemotherapeutic medication, is renowned for its cardiotoxic effects, which can cause left ventricular dysfunction or heart failure [7].

Chemotherapy is among the most effective cancer treatments. Chemotherapy suppresses cell division by using a variety of cytotoxic medicines, hormonal agents, protein kinase inhibitors, and monoclonal antibodies [8]. Anthracycline-induced cardiotoxicity is primarily caused by the formation of free radicals from doxorubicin via mitochondrial redox cycling in the cardiomyocyte, which eventually leads to left ventricular dysfunction and, in severe cases, congestive heart failure [9]. Trastuzumab is a recombinant humanized monoclonal antibody that targets the extracellular domain of the human epidermal growth factor receptor protein (HER2), which is overexpressed in 20-30% of breast tumors (BC) and is linked with an inadequate prognosis [11]. Trastuzumab targets HER2 receptors, which are present in both cardiomyocytes and tumor cells and play a role in cardioprotective processes under cell stress. Trastuzumab treatment can result in a decrease in LVEF and, in severe cases, heart failure (HF), especially when used alone or in combination with other cardiotoxic chemotherapies like anthracyclines [12].

The goal of the current study was to examine the cardiotoxicity associated with the use of doxorubicin and trastuzumab in HER-2 positive breast cancer patients, through a retrospective analysis.Materials and Methods Patients

Between September 2023 and February 2024, previous data of all consecutive patients presented to the medical oncology department of a tertiary care institution in south India who were diagnosed with HER-2 positive breast cancer and got therapy with doxorubicin and trastuzumab.

Study method

This was a retrospective observational study carried out in a tertiary care teaching institution. This study involved all of the subjects who met the inclusion and exclusion criteria. The data was examined and analyzed to determine the causes, incidence, and prevalence of cardiac toxicity. We compared the data collected and provided the results.

Statistical analysis

All data was collected, entered, and analyzed in a Microsoft Excel spreadsheet. The data was evaluated statistically and displayed using SPSS Software (version 28.0.1, released in November 2021 by IBM, Armonk, New York, United States). We used a student t-test with a significance level of P < 0.05 and a 95% confidence interval for all two-tailed analyses. Descriptive data were expressed as percentages.For the analysis of laboratory data ANOVA test, chi square test at p <0.05 with 95% confidence interval was used

Results

All data was collected, entered, and analysed using a Microsoft Excel spreadsheet. A total of 117 participants who met the inclusion criteria participated in the study. The data were shown as percentages, means, and standard deviations. The clinical features were analysed using a student t test. All tests were two-tailed, with a significance level of $p < 0.05$ and a 95% confidence range. The laboratory data was analysed using ANOVA and chi square tests at $p < 0.05$ with 95% confidence intervals.

Table 01 depicts the distribution of subjects aged 11-80 years. The subjects' mean age was 58.8 years, with a standard deviation of 14.345. The majority of the 117 patients were over 65 years old (40.1%), with the 45-65 age range accounting for 35.1%. There were no cases observed in the 11-17 age group. A t-test revealed a statistically significant correlation between age group and ductal cancer versus lobular cancer (t-value = -2.472, p-value = 0.03436).

Age groups	Ductal carcinoma (N=73)	Lobular carcinoma (N=44)	No. of Subjects (N=117)	Percentage (%)
11-17 yrs	0	0	0	0%
18-30 yrs	6	0	6	10.8%
31-45 yrs	9	6	15	13.50%
45-65 yrs	28	17	45	35.10%
>65yrs	30	21	51	40.51%
Paired t-test			t= -2.472	p= 0.03436

Table 01: Distribution of subjects based on age group and type of breast cancer

Figure 8 depicts the distribution of topic information by gender. It is significant that the majority of participants identified as females, representing 116 individuals (99.1%), whereas men comprised only one individual (0.8%).

FIGURE 01: Distribution of subjects based on Gender

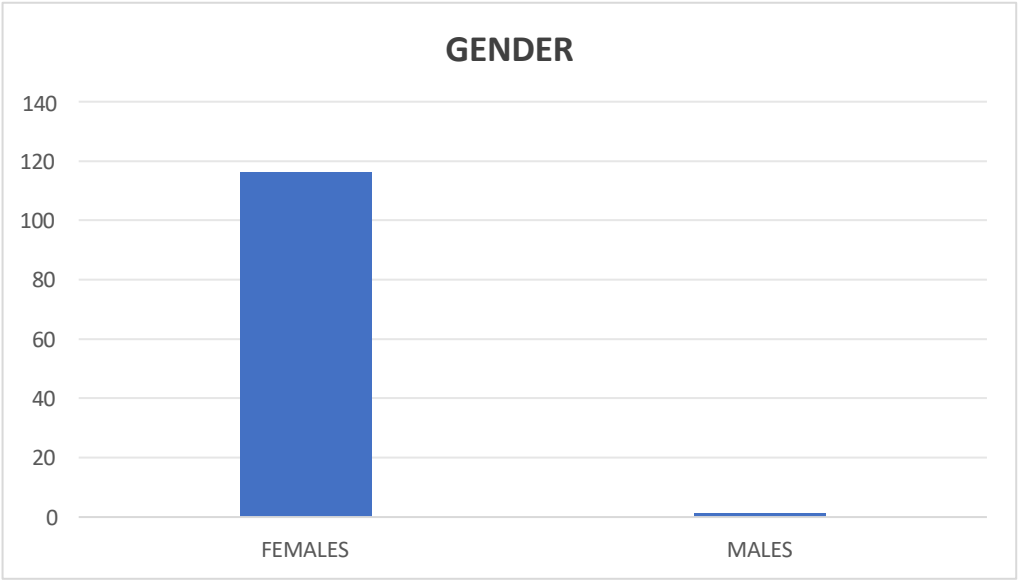

Table:02 shows the distribution of 117 patients with BMIs ranging from <18.4 kg/m2 to >40.0 kg/m2. The majority of the participants were within the BMI range of 30-34kg/m2 (53, 45.20%), followed by 35-39kg/m2 (27, 23.07%), with no subjects in the BMI range of <18.4kg/m2. This is graphically shown in Figure 9. A t-test was used to analyse the relationship between BMI and the occurrence of ductal cancer versus lobular cancer, and the results were statistically significant (t-value = -2.30347, p- value = 0.04131).

BMI	Ductal carcinoma(N=73)	Lobular rcinoma (N=44)	f Subjects (N=117)	entage (%)
<18.4	0	0	0	0%
18.5-24	8	5	13	11.11 %
25-29	15	9	24	20.51%
30-34	34	19	53	45.20 %
35-39	16	11	27	23.07%
Paired t-test			t= -2.303474	p= 0.04131

Table 02: Distribution of subjects according to BMI and type of breast cancer

Figure 02 shows the distribution of patients according on smoking information. The majority of the instances were discovered among non-smokers 84 (71.79%), followed by regular smokers 14 (11.9%), ex-smokers (11.11%), or 92, and occasional smokers 6 (5.12%). Breast cancer is usually seen in regular smokers among the age group >65 years, according to a two-way ANOVA test with F=4.728 and p value 0.02115.

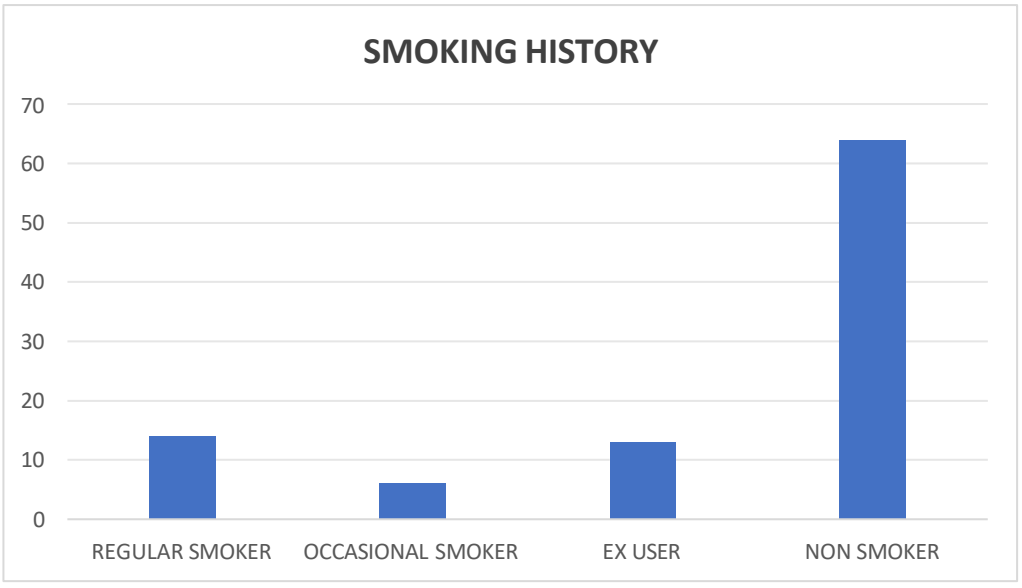

FIGURE 02: Distribution of subjects based on smoking habit

Distribution of subjects based on chief complaints information were depicted in table: 03. Majority of the cases were found within subjects of lump breast (99%) i.e., 116, followed by weight loss (55.7%) i.e., 66, inflammation in breast (87.3%) i.e., 92, nipple discharge (27.5%) i.e., 29, and breast pain (32.9%) i.e., 39.

CHIEF COMPLAINTS	BJECTS (117)	PERCENTAGE (%)
Lump in breast	116	99%
Weight loss	66	55.7%%
Inflammation in breast	92	87.3%
Nipple discharge	29	27.5%
Breast pain	39	32.9%

TABLE 03: Distribution of subjects based on chief complaints

Table 04 depicts the information regarding the distribution of subjects based on their menstrual history. Majority of subjects were experiencing late menopause (48%), i.e., 54 followed by early menarche (29.72%) i.e., 32, and then normal menarche (5.40%), i.e, 5 which is graphically represented in the Figure-16.The association between menstrual history and the occurrence of ductal cancer versus lobular cancer was assessed using a t-test, yielding a statistically significant result with a t-value of -2.35907 and a p-value of 0.03887. The economic status distribution is visually depicted in Figure 16.

MENSTRUATION	Ductal carcinoma (N=73)	Lobular rcinoma (N=44)	No. of Subjects (N=117)	ntage (%)
LATE MENOPAUSE	31	24	54	48%
EARLY MENARCHE	19	13	32	29.72%
LATE MENARCHE	7	6	13	9%
MENOPAUSE	6	5	11	8.3%
NORMAL MENARCHE	3	2	5	5.40%
Paired t-test			t= -2.35907	p= 0.03887

Table 04: Distribution of subjects based on menstrual history and type of breast cancer

The table 05 displays the distribution of subjects based on their hormonal receptor status. Out of the total 117 subjects, 73 had ductal carcinoma and 44 had lobular carcinoma. All 117 subjects were HER2 positive (100%), indicating positivity in both ductal and lobular carcinoma patients. Among ductal carcinoma subjects, 68 were ER positive, and among lobular carcinoma subjects, 28 were ER positive, totaling 82.05% (96). For PR positivity, 59 ductal carcinoma subjects and 39 lobular carcinoma subjects were positive, totaling 83.76% (98).

EGFR positivity was observed in 71 ductal carcinoma patients and 34 lobular cancer patients, totaling 89.74% (105).

HORMONAL RECEPTOR	arcinoma (N=73)	Lobular rcinoma (N=44)	No of subjects (N=117)	ercenta ge (%)
HER2 Positive	73	44	117	100%
ER positive	68	28	96	82.05%
ER negative	21		21	17.94%
PR positive	59	39	98	83.76%
PR negative	19		19	16.23%
EGFR Positive	71	34	105	89.74%
EGFR Negative	12		12	10.25%

TABLE 05: Distribution of subjects based on Hormonal receptors

The below table 07 shows that the subjects were divided into 2 chemotherapy regimen groups. Among them 61 subjects are given with trastuzumab only chemotherapy in which 34(29.05%) subjects were given a dose of 8mg/kg once for every 3 weeks. 27(23.07%) subjects were given a dose of 2mg/kg weekly. A group of 56(47.86%) subjects were given doxorubicin only therapy at a dose of 50mg/kg week

TRASTUZUMAB	
DOSE	NO OF SUBJECTS(117)
1)8mg/kg 3 rd week	(34)29.05%
2)2mg/kg weekly	(27)23.07%
DOXORUBICIN	
50mg/kg weekly	(56)47.86%

Table 07: Distribution of subjects based on treatment undergone chemotherapy

The distribution of subjects based on ejection fraction (2D ECHO) before and after treatment with doxorubicin is shown in Figure-17. Out of 117 subjects, 56 received doxorubicin treatment. Before

treatment, the majority of cases had a normal ejection fraction (EF) in 51 subjects, while an EF of 41-49% was observed in 6 subjects. After treatment, 17 subjects had a normal EF, an EF of 41-49% was observed in 19 subjects, 30-40% in 14 subjects, and <30% in 6 subjects. The p-value was 0.000017, indicating statistical significance.These results are graphically represented in Figure-17

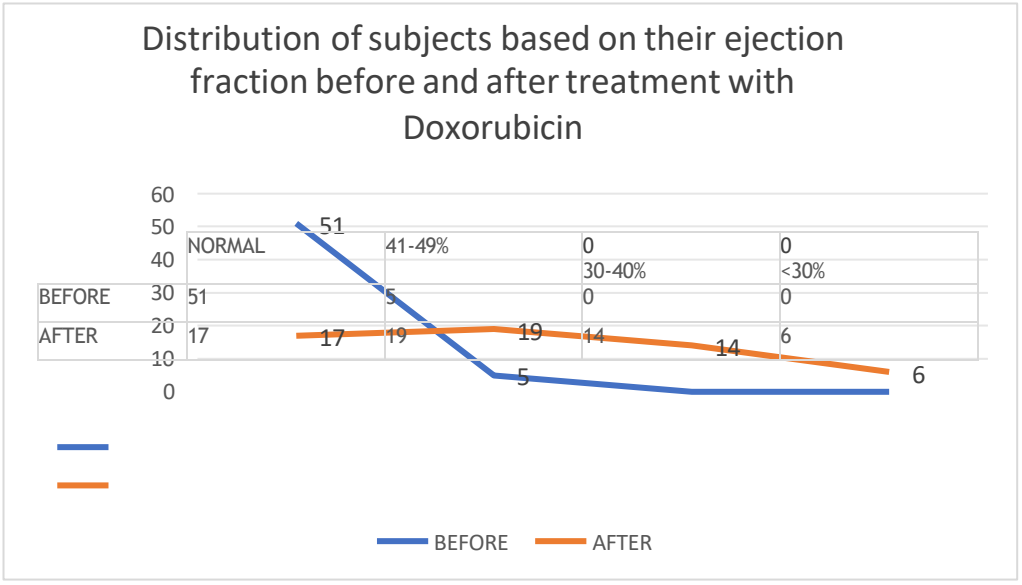

Figure-03: Distribution of subjects based on their ejection fraction before and after treatment with doxorubicin

The distribution of subjects based on ejection fraction (2D ECHO) before and after treatment with trastuzumab 2mg is shown in Figure-04. Out of 117 subjects, 27 received trastuzumab 2mg treatment. Before treatment, the majority of cases had a normal ejection fraction (EF) in 19 subjects, while an EF of 41-49% was observed in 8 subjects. After treatment, 13 subjects hada normal EF, an EF of 41-49% was observed in 11 subjects, 30-40% in 2 subjects, and <30% in 1 subjects. The p-value was 0.2035, indicating no statistical significance.These results aregraphically represented in Figure-04

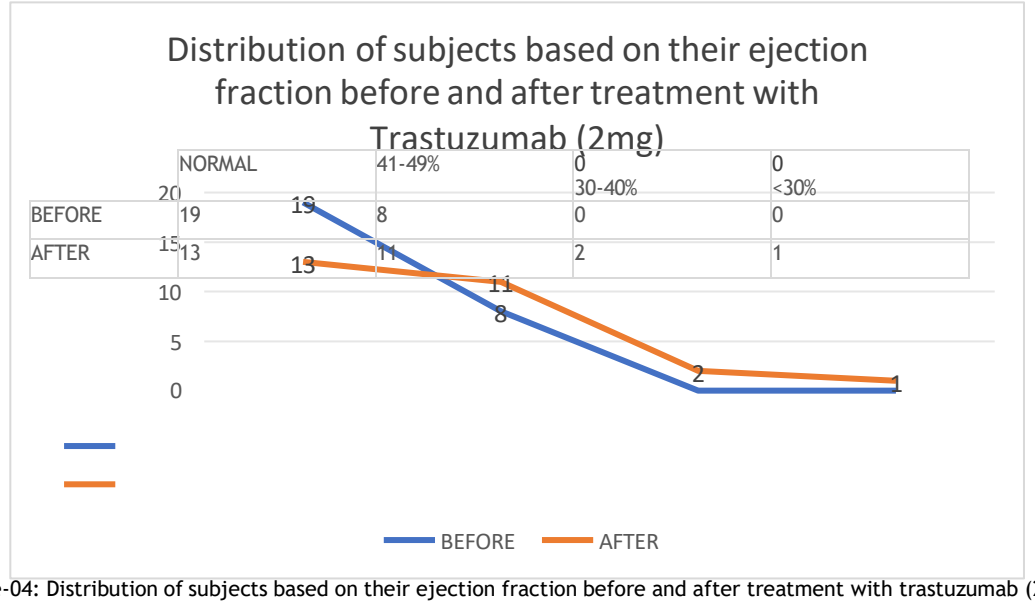

Figure-04: Distribution of subjects based on their ejection fraction before and after treatment with trastuzumab (2mg)

The distribution of subjects based on ejection fraction (2D ECHO) before and after treatmentwith trastuzumab 8mg is shown in Figure-5. Out of 117 subjects, 34 received trastuzumab 8mg treatment. Before treatment, the majority of cases had a normal ejection fraction (EF) in 27 subjects, while an EF of 41-49% was observed in 7 subjects. After treatment, 8 subjects had anormal EF, an EF of 41-49% was observed in 14 subjects, 30-40% in 9 subjects, and <30% in3 subjects. The p-value was 0.000018, indicating statistical significance. These results are graphically represented in Figure-05

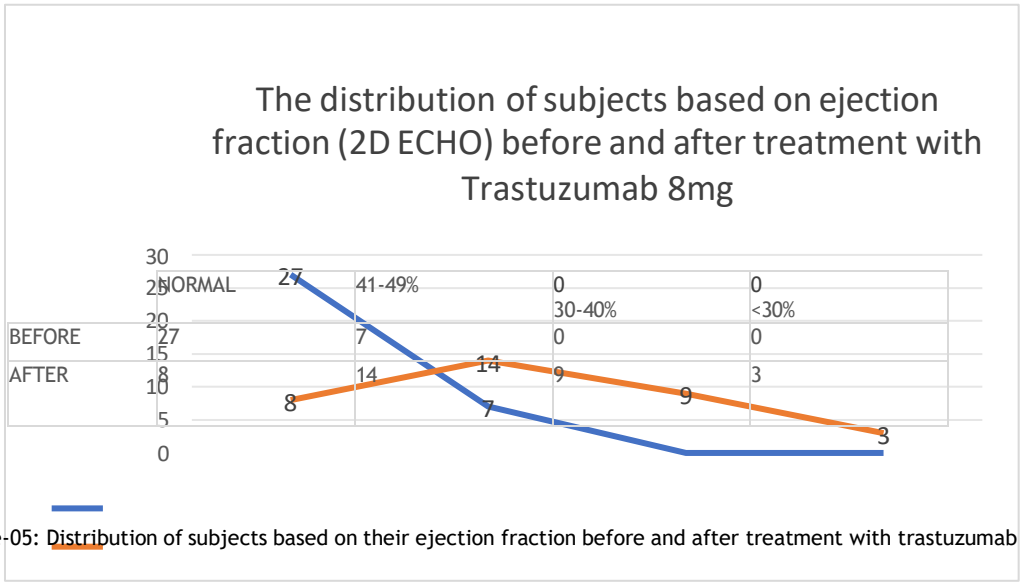

Figure-05: Distribution of subjects based on their ejection fraction before and after treatment with trastuzumab (8mg)

DISCUSSION

Breast cancer is a prevalent cancer in women, with HER-2 positive subtypes causing aggressive disease and poor prognosis. Treatment often involves chemotherapy, targeted therapy, and trastuzumab. However, Doxorubicin, a chemotherapeutic medication, can cause cardiotoxicity, leading to left ventricular dysfunction or heart failure. Cardiotoxicity can cause cardiomyopathy, heart failure symptoms, tachycardia, and a minimum LVEF of less than 55% accompanied by heart failure symptoms. Understanding the diverse clinical spectrum of this disease is essential for optimizing patient care and outcomes.This is a retrospective observational study which was carried out on the "A RETROSPECTIVE ANALYSIS OF CARDIOTOXICITY WITH DOXORUBICIN AND TRASTUZUMAB IN BREAST CANCER HER-2 POSITIVE
PATIENTS".117 participants were added to the study upon passing the inclusion requirements. The data gathered was computed, tabulated, and evaluated.

According to our study, comprising 117 patients, the mean age was determined to be 58.4 years. A t-test showed a t-value of -2.472 and a p-value of 0.03436. Another study by Mariana Chavez- MacGregor involved 3,983 patients, with a median age of 71.7%. Erika Matos' research involved exclusively female patients, with an average age of 53.6 years.

Anjali Aggarwal conducted research involving 64 female breast cancer patients at a tertiary care facility in India from 2015 to 2018[43]. In our investigation, out of 117 participants, 116 were female patients, and one was male. A study by Nashwa Abdel-Aziz found a significant correlation between BMI and cardiotoxicity in patients receiving anthracycline and trastuzumab combined. BMI ranged from <18.4 kg/m² to >40.0 kg/m², with approximately 45.2% of patients falling into the 30-34 kg/m² range. In a study of 117 patients, the correlation was p=0.04, indicating a significant association between BMI and cardiotoxicity risk.

Johnson et al. conducted research in which dyspnea was experienced by 50% of individuals with cardiotoxicity in breast cancer[44]. According to Smith et al., 40% of individuals with cardiotoxicity reported having chest pain[45]. In our study with 117 participants, we observedthat 99.1% of patients reported lumping the breast.

A study by Martinez et al. discovered that smokers were more likely than nonsmokers to develop cardiotoxicity [50].In our investigation, that breast cancer is more common among regular smokers over 65 years old, with a statistically significant association with cardiotoxicity, according to a two-way ANOVA test with an F-value of 4.728 and a p- value of 0.02115. The majority of cases involved non-smokers, followed by regular smokers and occasional smokers.

In 2020, Smith and colleagues conducted a study that revealed that women who had a history of irregular menstrual cycles Were prone to experiencing cardiotoxicity after receiving doxorubicin treatment for breast cancer with a p-value of 0.04 [45]. In our study involving 117 participants, we observed that the most common menstrual history was late menopause, reported by 48% of the participants, followed by early menarche at 29.72% and normal menarche at 5.40%. The statistical analysis revealed a p-value of 0.03, indicating a significant association between menstrual history and the risk of cardiotoxicity in these patients.

Research indicates that patients with high EGFR expression are more likely to experience cardiotoxicity when receiving doxorubicin and trastuzumab. However, no significant connection was found between EGFR expression and cardiotoxicity in a similar patient cohort. ER-positive individuals were more likely to develop cardiotoxicity than ER-negative patients. Garcia et al. found that ER-positive patients were less likely to suffer cardiotoxicity. Amanda Z's meta-analysis revealed a significant association between PR status and cardiotoxicity in HER-2-positive breast cancer patients. Brown et al. found a strong link between HER2 positive and a higher risk of cardiotoxicity. In our study of 117 subjects, 73 had ductal carcinoma and 44 had lobular carcinoma, all 117 were HER2positive (100%), indicating positivity in both ductal and lobular carcinoma patients.

Alghafar DA conducted a study that found that 35 patients (24%) experienced trastuzumab- induced cardiotoxicity, with 83% stopping the medication temporarily. It showed a significant association of cardiotoxicity (p-value: 0.009). [51]. Smith et al. conducted a prospective cohort study to assess the effectiveness of 2DECHO in detecting cardiotoxicity in HER-2- positive breast cancer patients receiving doxorubicin and trastuzumab [45]. HE discovered that changesin left- ventricular-ejection-fraction (LVEF) on follow-up 2DECHO were predictive of future cardiotoxicity, with a drop of more than 10% from baseline related to an increased risk of cardiac events (p-value: 0.0025) [45]. In a study involving 117 participants, 56 were treated with doxorubicin, 27 with trastuzumab 2mg, and 23 with trastuzumab 8mgs, out of 117 subjects, 56 received doxorubicin treatment. Before treatment, 51 subjects exhibited a normal EF, while6 had an EF of 41-49%. Following treatment, 17 subjects had a normal EF, 19 had an EF of 41- 49%, 14 had an EF of 30-40%, and 6 had an EF <30%. The p-value was 0.000017, indicating statistical significance. 27 received this treatment with trastuzumab 2mg. Before treatment, 19 subjects had a normal EF, and 8 had an EF of 41- 49%. After treatment, 13 had anormal EF, 11 had an EF of 41-49%, 2 had an EF of 30-40%, and 1 had an EF <30%. The p-value was 0.2035, indicating no statistical significance. 4 received this treatment trastuzumab 8mg. Before treatment, 27 subjects had a normal EF, while 7 had an EF of 41-49%.

Followingtreatment, 8 had a normal EF, 14 had an EF of 41- 49%, 9 had an EF of 30-40%, and 3 had an EF <30%. The p-value was 0.000018, indicating statistical significance.

In our study, of 117 subjects, 11 of them had passed away. Among the remaining 106subjects, 7 chose to discontinue treatment and are now receiving therapy in their hometowns.

Our current analysis focuses on the follow-up of 99 subjects, with 61 subjects successfully cured and the remaining 38 still undergoing chemotherapy.

CONCLUSION

In conclusion, our findings highlight numerous crucial parameters that are strongly linked with cardiotoxicity in HER-2-positive breast cancer patients treated with doxorubicin and trastuzumab. Key findings include a mean patient age of 58.4 years, with a significant association between age groups and cancer type. We found a strong correlation between BMI and cardiotoxicity risk, with a significant proportion of patients falling within the 30-34 kg/m² range. Ejection fraction significantly impacts cardiotoxicity risk, particularly for individuals with smaller ejection fractions, especially after receiving doxorubicin, trastuzumab 8mg, and trastuzumab low doses don't show any significance about cardiotoxicity. Understanding these factors is crucial for risk stratification and the development of personalized treatment strategies to minimize the risk of cardiotoxicityand improve outcomes in this patient population. Further research is needed to validate these findings and explore additional factors that may influence cardiotoxicity in HER-2-positive breast cancer patients.. However, trastuzumab 8mg and low doses do not show significant cardiotoxicity risk. Further research is needed to validate these findings and explore additional factors influencing cardiotoxicity in HER-2-positive breast cancer patients.

LIMITATIONS:

This study contains a small sample size. So, this can be further extended with number of patients to derive a better conclusion.

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