Trastuzumab cardiotoxicity in HER2-positive breast cancer patients in tertiary health care center, sultanate of Oman

Abd Alghafar, D., Younos, I., Al Baimani, K., Al-Salhi, D., Al-Riyami, A., Rizvi, S., & Buckley, N. E. (2020). Trastuzumab cardiotoxicity in HER2-positive breast cancer patients in tertiary health care center, sultanate of Oman. *Journal of Oncology Pharmacy Practice*. Advance online publication. https://doi.org/10.1177/1078155220919888

Published in:
Journal of Oncology Pharmacy Practice

Document Version:
Peer reviewed version

Queen's University Belfast - Research Portal:
Link to publication record in Queen's University Belfast Research Portal

Journal of Oncology Pharmacy Practice

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Journal:	*Journal of Oncology Pharmacy Practice*
Manuscript ID	JOPP-19-0474.R1
Manuscript Type:	Original Article
Keywords:	Trastuzumab, Cardiotoxicity, HER2, Breast Cancer, chemotherapy

Abstract:

Trastuzumab, a monoclonal antibody, targeting the human epidermal growth factor receptor 2 (HER2), is used to treat breast cancer in patients harboring amplification of the HER2 locus. Cardiotoxicity is a common side effect of trastuzumab that leads to discontinuation of treatment in a significant proportion of cancer patients.
In our retrospective study, we evaluate the prevalence and identify the risk factors for cardiotoxicity associated with trastuzumab in HER2-positive breast cancer patients attending to Sultan Qaboos University Hospital between 10/2012 and 10/2017. Using patient records, we collected patients' characteristics (age, menopausal status, lymph nodal status, distant metastasis at presentation, grade of tumor, comorbidities (diabetes mellitus, hypertension, coronary artery disease diseases)), chemotherapy received and total dose of trastuzumab as well as cardiotoxicity (including timing). Cardiotoxicity was defined based on the ejection fraction dropping by 10% of the original value or a drop in the ejection fraction below the normal value. Among the 146 patients included in the study, 35 showed trastuzumab-induced cardiotoxicity (TIC) (24%). Twenty-nine (83%) of those patients stopped trastuzumab temporarily. None of the cardiac risk factors, such as history of coronary artery disease, hypertension and diabetes, altered the risk of TIC. Previous anthracyclines therapy exposure increased the risk of TIC significantly ($p=0.009$). None of the other covariates influenced the incidence of TIC, which can be related to the relatively small sample size. Further studies are warranted to establish ways to predict, prevent, and treat TIC to provide patients with maximal therapeutic benefit.

Abstract

Trastuzumab, a monoclonal antibody targeting the human epidermal growth factor receptor 2 (HER2), is used to treat breast cancers harboring amplification of the HER2 locus. Cardiotoxicity is a common side effect of Trastuzumab that leads to discontinuation of treatment in a significant proportion of cancer patients.

In our retrospective study, we evaluate the prevalence and identify the risk factors for cardiotoxicity associated with Trastuzumab in HER2-positive breast cancer patients attending to Sultan Qaboos University Hospital between 10/2012 and 10/2017. Using patient records, we collected patients' characteristics (age, menopausal status, lymph nodal status, distant metastasis at presentation, grade of tumor, comorbidities (diabetes mellitus, hypertension, coronary artery disease diseases)), chemotherapy received and total dose of Trastuzumab as well as cardiotoxicity (including timing). Cardiotoxicity was defined based on the ejection fraction dropping by 10% of the original value or a drop in the ejection fraction below the normal value. Among the 146 patients included in the study, 35 showed Trastuzumab-induced cardiotoxicity (TIC) (24%). Twenty-nine (83%) of those patients stopped Trastuzumab temporarily. Risk of TIC was not altered by common cardiac risk factors such as history of coronary artery disease, hypertension and diabetes. Previous anthracyclines therapy exposure increased the risk of TIC significantly (p=0.009). None of the other covariates influenced the incidence of TIC, which may be related to the relatively small sample size. Further studies are warranted to establish ways to predict, prevent, and treat TIC to provide patients with maximal therapeutic benefit.

Keywords

Trastuzumab, Cardiotoxicity, HER2, Breast Cancer, Chemotherapy

List of Abbreviations

5-FU: 5-Fluorouracil
AC: Doxorubicin and Cyclophosphamide
ACEIs: Angiotensin-converting enzyme inhibitors
ARBs: Angiotensin Receptor Blockers
BBs: Beta Blockers
BC: Breast Cancer
BMI: Body Mass Index
CAD: Coronary Artery Disease
CDRs: Complementary determining regions
CoMHS: College of Medicine and Health Sciences
CMF: Cyclophosphamide, Methotrexate and 5-Fluorouracil
CMR: Cardiac magnetic resonance imaging.
DM: Diabetes Mellitus
ECHO: Echocardiogram
ER: Estrogen Receptor
FEC: 5-Fluorouracil plus Epirubicin plus Cyclophosphamide
HER2: Human Epidermal growth factor Receptor 2
HF: Heart Failure
LVEF: Left ventricular Ejection Fraction
mAb: Monoclonal Antibody
MBC: Metastatic Breast Cancer
MUGA: Multigated Radionuclide Angiography
muMAb: Murine Monoclonal Antibody
OCP: Oral Contraceptives
PI3K: Phosphoinositide 3-kinase
PR: Progesterone Receptor
SQUH; Sultan Qaboos University Hospital
TIC: Trastuzumab-Induced Cardiotoxicity

Introduction

Understanding the biology of breast cancer (BC) has helped to identify the human epidermal growth factor receptor 2 (HER2), encoded by the HER2 gene which is amplified and overexpressed in 15-20% of breast cancers and associated with tumor proliferation, migration, and differentiation through its involvement in the activation of the PI3K/Akt and Ras/-Raf/MEK/MAPK pathways. [(1)] HER2 amplification is also associated with incomplete resistance to hormonal therapy, improved response to anthracycline-containing chemotherapy regimens and poor response to Cyclophosphamide, Methotrexate and 5-Fluorouracil (CMF) chemotherapy combination. [(2)]

In late 1990s, a humanized monoclonal antibody targeting the extracellular domain of HER2, Trastuzumab, was approved for treatment of patients with HER2 positive metastatic BC. [(3-5)] This humanized form of muMAb-4D5 was engineered by grafting the antigen binding loops of the hypervariable CDRs to a human IgG_1 framework. [(6)] Trastuzumab was investigated in numerous preclinical studies in HER2 positive BC cell lines and xenograft models in immunodeficient mice, revealing anti-tumour activity as a monotherapy and in combination with several chemotherapeutic agents involving, thiotepa, cisplatin, paclitaxel, vinblastine, doxorubicin, methotrexate and etoposide. [(7)]

The mechanism of action of Trastuzumab in BC treatment is is complex and multifactorial and not completely understood. (8) Proposed mechanisms include PI3K pathway inhibition, (9) promotion of an immune-mediated response, (10-12) inhibition of HER2-ECD cleavage, (13-15) promotion of HER2-receptor downregulation, (16,17) induction of cell cycle arrest through post-translational upregulation of $p27^{kip1}$ (18) and inhibition of angiogenesis (19,20).

As preclinical Trastuzumab studies suggested that HER2 played an essential role in the developing embryonic heart and is important for maintaining cardiac function in the adult heart, (21) there were considerable concerns regarding its cardiotoxicity in early clinical trials (22). It is believed that Trastuzumab-induced cardiotoxicity (TIC) is the result of a 'dual-hit' mechanism; it directly inhibits antiapoptotic pathways and upregulates angiotensin II, a potent vasoconstrictor, leading to an increase in the reactive oxygen species production and inhibition of neuregulin signaling, an important role in the regulation of cardiac structure and function. (23)

TIC ranges from asymptomatic left ventricular dysfunction to chronic heart failure (HF). (24) Although the primary risk for TIC is reportedly the combination with anthracycline-based chemotherapy, (25,26) a number of other TIC risk factors have been described. These include treatment duration, (24, 27,28) heavy alcohol consumption during treatment and history of diabetes mellitus (DM) (29, 30) or cardiovascular disease (25,29,31, 32). None of these risk factors can precisely predict occurrence and it is

important to note that patients with these risk factors were excluded from the majority of clinical trials.

Although TIC has become better understood (given increased experience with this agent) and risk factors identification, appropriate monitoring and treatment procedures are well-established, TIC incidence and associated risk factors have not yet been studied in Oman. This knowledge would improve predictability and contribute to a better population-based selection for Trastuzumab-containing regimens in HER2 positive BC in the Omani population.

In this study, we evaluate the incidence and risk factors related to TIC in patients with HER2 positive BC within different Trastuzumab treatment settings. We also determine and assess treatments used for alleviating TIC and rates of cardiac function recovery.

Methods

Study Design and Settings

This is a single center retrospective cohort study. Using an institutional medical records database, all early and advanced BC patients treated with Trastuzumab were identified at Adult Medical Oncology Unit, SQUH, Muscat, Oman, from 1 October 2012 to 1 October 2017. 146 patients were identified and were eligible for the study.

Inclusion Criteria

- HER2 positive BC patients.
- Adult age group including both women.
- High quality baseline 2D-echocardiogram (ECHO) and LVEF ≥ 50%.
- Treatment with Trastuzumab as monotherapy or Trastuzumab-containing regimen.
- Available information on Trastuzumab dosing and clinical outcomes.

Exclusion Criteria

- Patients with previous cancer before their first diagnosis of BC.
- Life expectancy ≤ 12 weeks.
- Age ≤ 18 or ≥ 75 years.
- Patients with incomplete data.

Ethical Approval

Ethical approval (# 1661) was granted by the Medical Research Ethics Committee (MERC) at SQU, CoMHS before starting the study. Confidentiality was strictly maintained throughout the study.

Data Collection

The following data were extracted retrospectively from electronic medical records for each patient: age, gender, tumor characteristics, body mass index, BC side, use of radiation therapy, menopausal state, Trastuzumab schedule, Trastuzumab cumulative dose, estrogen and progesterone receptor status, cardiac risk factors (DM, hypertension, hypercholesterolemia and ischemic heart diseases), use of antihypertensive and statins medications, previous chemotherapy received, concurrent chemotherapy, concurrent pertuzumab, concurrent hormonal treatment, timing of cardiotoxicity, treatment used to alleviate cardiotoxicity and EF recovery rates after cardiotoxicity. In addition, we collected data regarding presentation with HF symptoms or asymptomatic and re-challenge rate.

Cardiac risk factors included hypertension (defined as blood pressure >140/90 mm Hg maintained over time or use of antihypertensive drugs), dyslipidemia (defined as total plasmatic cholesterol > 5.2 mmol/L or use of lipid-lowering medications), DM (diagnosed as fasting serum glucose ≥ 7.0 mmol/L 2-h post challenge serum glucose ≥ 11.1 mmol/L or use of hypoglycemic medications). All patients underwent a

comprehensive baseline cardiac examination and ECHO as part of their routine pre-chemotherapy evaluation. Both evaluations were repeated before starting Trastuzumab (baseline) and almost every 3 months thereafter for the duration of therapy.

Trastuzumab Regimens

Patients received Trastuzumab dose of 8 mg/ kg of body weight administered as a 90-minute intravenous infusion as loading dose, followed by maintenance doses of 6 mg/kg given every 3 weeks. Patients that completed the adjuvant treatment without interruption received 18 doses and the total length was approximately 1 year.

Trastuzumab was administered sequential to anthracyclines and patients with metastatic breast cancer (MBC) continue anti HER2 beyond progression.

Trastuzumab-induced Cardiotoxicity (TIC) Definition and Monitoring

TIC was defined according to the criteria followed by Herceptin Adjuvant (HERA) clinical trial as symptomatic (e.g., HF and/or dyspnea, and/or referral to a cardiologist for confirmation) or asymptomatic (e.g., decline in LVEF > 10% from baseline or LVEF < 50%) [33]. Cardiac monitoring to determine LVEF was performed every 3 months using serial MUGA or an ECHO at the discretion of the treating medical oncologist.

Statistical Analysis

Descriptive statistics were used to describe the number of patients experiencing a LVEF reduction. Significance of differences between mean values was evaluated using Independent Student's two-sample *t*-test, (SPSS 23.0, Inc., Chicago, IL). Correlation analyses were undertaken using chi-square analysis. Data were presented as mean ± SEM. Significance was assumed at p value of ≤ 0.05.

Results

The characteristics of the patients included in the study are summarized in **Table 1**. The study population included 146 patients (range 29–74 years, mean age of 48.10±10 years and mean BMI of 29.44) who received Trastuzumab in a neoadjuvent, adjuvant, pseudoadjuvent (chemotherapy given as adjuvant after resection of locoregional recurrence) and/or palliative settings. As shown in **Table 2**, there was a low prevalence of preexisting DM, dyslipidemia, CAD and hypertension. All patients were New York Heart Association (NYHA) functional class I at baseline. All patients were diagnosed with BC with HER 2 amplification, fulfilling the American College of Physicians (ACP)/American Society of Clinical Oncology (ASCO) criteria for treatment with anti HER2 agent, mainly Trastuzumab.

In this study, cardiotoxicity was more common in patients receiving beta blockers (BBs) (**Figure 1**) but was less in patients receiving statins and equivocal in patients receiving and not receiving ACEIs **(Figure 1)**. In relation to menopausal status, cardiotoxicity was more common in patients with pre-menopausal status **(Table 2)**. In addition, proportion of patients who developed cardiotoxicity was equivocal in patients with metastatic BC and with those without metastatic diseases **(Table 2)**. Ptients with right-sided BC developed less cardiotoxicity compared to those with cancer on the left side **(Table 2)**. Additionally, cardiotoxicity was high in patients with PR+ disease compared to those with PR- or ER+/PR+ disease **(Table**

2). The majority of patients received anthracycline-based chemotherapy regimens containing either doxorubicin or epirubicin. Cardiotoxicity was significantly higher in patients receiving doxorubicin compared to those who do not receive anthracyclines or epirubicin or both and there was significant association between doxorubicin administration and TIC (p=0.009) (**Table 2**). Concurrent Taxanes and Pertuzumab administration was not significantly associated with cardiotoxicity **(Table 2 and 4)**. A non-significant trend was observed for the association between radiotherapy and cardiotoxicity with lower cardiotoxicity in patients not receiving radiotherapy **(Table 2)**. While a pre-existing history of hypertension was more common in those patients who developed TIC **(Table 1),** a pre-existing history of dyslipidemia, CAD and DM was less common in those patients who developed TIC **(Table 1)**.

For the population with preserved LVEF, all patients in the adjuvant setting received a total of 12 months of Trastuzumab treatment while patients in the palliative setting received Trastuzumab indefinitely unless other anti-HER2 agents were given. For the population who developed LV systolic dysfunction, the mean duration of treatment with Trastuzumab was 3 ± 4.5 months. The mean LVEF for the total population was 63.9 ± 5.3 on ECHO. In patients who developed symptomatic cardiomyopathy (n=15, 42.85%), symptoms were exertional dyspnea, orthopnea, fatigability, dyspnea, palpitation and chest pain with 1 patient died from Trastuzumab-induced HF. TIC was also diagnosed in asymptomatic patients (n=20,

57.14%) based on changes in LVEF levels. Both groups received appropriate HF medications including ACEIs/ARBs (100%) and BBs (70%) **(Table 2).**

Of the 35 patients who developed cardiotoxicity, 1 patient died due to disease progression, 5 patients completed their Trastuzumab treatment without interruption as they were at the end of the therapy and 29 patients temporary discontinued Trastuzumab therapy. Following the temporary discontinuation of Trastuzumab, all 29 patients underwent serial MUGA and ECHO at the time of diagnosis of cardiac dysfunction as well as 3 and 6 months post-diagnosis. Most of patients who developed cardiotoxicity recovered after treatment (n=22, 62.85%) with mean LVEF 54.79%, and 13 patients were re-challenged with the same dose of Trastuzumab with a mean re-challenge time of 5.4 months. **(Table 3)**

Discussion

Although Trastuzumab is not known to cause the classical toxicities associated with chemotherapy or other targeted therapy medications, one of the major concerns is the occurrence of cardiac dysfunction. Therefore, this study was designed with the aim of identifying the potential risk factors for cardiac toxicity associated with Trastuzumab treatment among Omani patients with HER2 positive BC.

This study contributes to the growing volume of literature reporting higher incidences of TIC compared to that reported within randomized controlled trials (RCTs) that led to Trastuzumab approval. In the HERA and NSABP-31 RCTs symptomatic TIC was reported as 2.1% and 5% respectively. (34) Moreover, TIC incidence of 23.97% at tertiary hospital in Oman is similar to results in other retrospective studies from various countries that reported 16%, 21% and 24% in USA, Israel and Canada respectively. (35-37) However, the TIC incidence in this study was lower compared to studies in Brazil reporting 33-53% (38-39).

One hypothesis to explain these differences between the "real world" and RCT incidence lies in the strict inclusion and wide exclusion criteria applied to RCTs. Contraindications to study entry in RCTs include patients with previously documented cardiac disease, adequate baseline hepatic, renal, and bone marrow function. Additionally, it is possible that the heterogeneity in the definition of asymptomatic TIC contributes to the differences between RCT and observational

studies. In the HERA RCT, decrease in LVEF was defined as a decline of ≥10% from baseline to LVEF < 50% at any time [40], while in the BCIRG 006 RCT, LVEF was defined as a relative reduction from baseline of more than 10% at the last evaluation [26]. Observational studies also vary in the definition of asymptomatic TIC from LVEF absolute reduction of ≥16–10% from baseline and drops in LVEF < 50–55%. [38,41]

In our study, a definition of asymptomatic TIC as a decline in LVEF ≥ 10% from baseline or LVEF < 50% was used based on HERA RCT [40]. The median time to development of TIC from Trastuzumab initiation in adjuvant setting was 8.5 months and 36 months in palliative setting.

In the current study, known cardiac risk factors were not associated with increased risk of TIC. This differs from the results of a a retrospective analysis of 218 metastatic BC patients who received Trastuzumab for at least 1 year from 1998 to 2003 where higher rates of TIC was associated with a history of DM[42]. However, a prospective cohort study by Matos et al. where 92 patients were studied for possible risk factors associated with TIC, DM or dyslipidemia did not appear to be associated with increased cardiomyopathy risk. [43] The difference in the results among these studies may be attributed to small samples size.

Patients in our study who used BBs for hypertension and CAD treatment showed significant association with TIC. This association could be a confounding to a preexisting heart disease rather than a true association. In fact, this observation was

not supported by other previous studies. On the contrary, there are other studies supporting the idea that BBs show favorable effects on preventing cardiotoxicity associated with Trastuzumab. [44] Hypertension, the most extensively studied co-morbidity in this patients' population, is a generally accepted risk factor and its importance was confirmed in several studies. [31] Nevertheless, the results are not uniform and there are studies that, like this study, could not demonstrate its predictive role. [45]

Additionally, we did not find that CAD was an important predictive factor of TIC, which is in contrary to the results obtained from a study performed by Xue and colleagues where they found that the risk of cardiotoxicity was more strongly associated with the history of CAD among patients treated with Trastuzumab. [46] However, there are other studies that could not confirm its predictive value such as the one performed by Tarantini and colleagues. [41]

While our patients' age and BMI were comparable to reported adjuvant studies [31,45,47], patients' age was not found as an important predictive factor in this study, which is in contrary to the results of two North American prospective randomized clinical studies [31,45]. On the other hand, there are studies that could not confirm its predictive value, among them the HERA study as well as "real-world" studies. [47-48] In the HERA study, [45] BMI was found to be important risk factor. However, this was not demonstrated or not extensively studied in another studies [31]. In this study, BMI did not emerge as important risk factor.

Due to the proximity of the heart in the chest wall, there is a hypothesis of the association between left-sided breast cancer with radiation and the development of TIC. Data from the NCCTG N9831 RCT investigated concomitant Trastuzumab and radiotherapy in 908 patients and found no significant differences between radiated and non-radiated groups. [49] A study by Cao et al. [50] reported that left-sided radiation with increased low-dose volume and mean heart dose was associated with reversible low-grade cardiac toxicity. In this study, there was no significant association between radiotherapy, left side breast tumor and TIC.

As treatment plans for BC patients are generally complex, with more than 1 modality, it is often hard to dissect the cardiotoxic effect of each individual regimen. These treatments may interact with each other and have added effect to the cardiovascular system. Indeed, this study found that previous anthracycline use is a significant risk factor for developing TIC (p=0.009) which is similar to the results obtained from a meta-analysis conducted by Jawa et al. 2016 [51-53].

For docetaxel containing regimen, a study conducted by Shimoyam and colleagues illustrated that docetaxel is a cardiotoxic agent that induces cardiac contractile dysfunction. [54] However, the results from Pegram et al. 2007 found that docetaxel/Trastuzumab containing regimen could offer clinical efficacy with a low risk of cardiac dysfunction. [4] In this study, docetaxel is trending towards a significant association with TIC (p=0.085). this may be attributed to its cardiotoxic effect as its mechanism of action is primarily related to its ability to increase

microtubule assembly and to stabilize microtubules by preventing their depolymerization, thus disrupting normal cell division. It has been shown that increased microtubule density, for which microtubule stabilization is one potential mechanism, causes contractile dysfunction in cardiac hypertrophy.[54]

Studies showed that TIC seems to be reversible when Trastuzumab is withdrawn. [55, 56] Twenty-nine (82.85 %) patients who discontinued the treatment in our study recovered from the cardiac events **(Table 3)**. Another study showed a lower percentage (9.4 %) of recovery. [54] However, both studies lack a more rigorous investigation of the long-term effects of this anticancer therapy in order to verify TIC reversibility. Treatment discontinuation and/or management of cardiovascular side effects with cardio protective agents such as ACEIs or diuretics are recommended strategies to revert TIC and all 35 patients within this cohort received cardiovascular medications after the development of TIC. However, there are clinical studies showed that the discontinuation of Trastuzumab alone is able to restore cardiac function and/or prevent cardiac events in patients with a decrease in LVEF lower than 40 %. [42] This finding suggests that there is a need to combine efforts between oncologists and cardiologists to determine which patient that developed TIC actually require the cardiovascular medication.

This study has several limitations associated with its retrospective nature. Given the small sample size, there were limitations in statistical power to perform further exploratory analyses. There were limitations by the quality of information

available from the electronic medical records and other potential variables such as physical inactivity. Cardiac biomarkers such as Troponin-I and B-type natriuretic peptide, were not collected as they are not part of the standard-of-care. LVEF assessments were also conducted with MUGA or ECHO, adding inter-study and inter-operator variability across different tests. Additionally, this study was limited by the short follow-up time and therefore cannot determine the long-term incidence of TIC.

Conclusions

To our knowledge, this investigation is the first retrospective study conducted in Oman to assess the incidence of TIC, the rate of Trastuzumab discontinuation and to investigate possible factors associated with TIC in clinical practice. This study showed a moderate incidence of TIC among HER2 positive breast cancer patients (24%) and that there is a need of a closer cardiac monitoring to prevent cardiac complications in this population.

Although 5 patients finished the treatment without interruption, 29 patients discontinued the therapy temporary, suggesting that it is important to stimulate collaboration between cardiologists and oncologists to outweigh the risks of this anticancer therapy and to identify patients that need cardiovascular medication after developing TIC. In addition, previous BBs and anthracyclines use were significantly associated with TIC in this population. However, no cardiovascular risk factors were independently associated with TIC. Larger studies should be conducted in order to confirm which specific factors are associated with the development of TIC to early identify potential cardiovascular injury and to establish strategies to prevent TIC among this population.

Funding Acknowledgements

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Declaration of conflicting interests

The Authors declare that there is no conflict of interest.

Tables

Table 1:
Sociodemographic and clinical characteristics of the studied population

Total patients (146)	n (%)
Age group (years)	
< 35	15 (10.27 %)
35–49	72 (49.31 %)
50–59	32 (21.91 %)
> 60	27 (18.49 %)
BMI	
< 20	6 (4.10 %)
20–24	29 (19.86 %)
25–29	55 (37.67 %)
> 30	56 (38.35 %)
Cardiac risks	
Hypertension	68 (46.58 %)
Diabetes mellitus	34 (23.29 %)
Dyslipidemia	32 (21.92 %)
CAD	10 (6.85 %)
Cardiovascular medications	68 (46.58 %)
Radiotherapy	120 (82.19 %)
Tumor location	
Left	80 (54.79 %)
Right	66 (44.52 %)
Bilateral	0
Menopausal Status	
Pre-menopausal	91 (62.32 %)
Post-menopausal	55 (37.67 %)
Hormone receptor status	
ER – PR -	60 (41.09 %)
ER + PR -	10 (6.8 %)
PR + ER -	2 (1.36 %)
ER + PR +	74 (50.68 %)
Stage	
I	7 (4.79 %)
II	39 (26.71 %)
III	63 (43.15 %)
IV	37 (25.34 %)
Chemotherapy regimen	
AC	88 (60.27 %)
FEC	20 (13.69 %)
Others	37 (26.04 %)
Radiotherapy	120 (82.19 %)
Family history of cancer	13 (8.9 %)
Cardiovascular medication	
Beta blocker	35 (23.97 %)
ACE inhibitors	29 (19.86 %)

Statins	32 (21.91 %)
Anthracycline-based chemotherapy	
Treatment without anthracyclines	48 (32.88%)
Epirubicin	10 (6.8 %)
Doxorubicin	78 (53.42 %)
Both Doxorubicin and Epirubicin	10 (6.8 %)

BMI: Body Mass Index, ER: Estrogen Receptor, PR: Progesterone Receptor, AC: Doxorubicin plus Cyclophosphamide, FEC: 5-Fluorouracil plus Epirubicin plus Cyclophosphamide.

Table 2:
Factors associated with Trastuzumab-induced cardiotoxicity

	TIC		
	Yes (n = 35)	**No (n = 111)**	***p* value**
Age group (years)			
< 35	3 (20%)	12 (80%)	1.000
35–49	21 (29.2%)	51 (70.8%)	0.176
50–59	8 (25%)	24 (75%)	1.000
> 60	3 (11.1%)	24 (88.9%)	0.132
BMI			
< 20	1 (16.7%)	5 (83.3%)	1.000
20–24	6 (20%)	24 (80%)	0.639
25–29	13 (24.5%)	40 (75.5%)	1.000
> 30	15 (26.3%)	42 (73.7%)	0.692
Cardiac risks			
Hypertension	19 (27.9%)	49 (72.1%)	0.334
Diabetes mellitus	6 (17.6%)	28 (82.4%)	0.369
Dyslipidemia	6 (18.8%)	26 (81.3%)	0.492
CAD	2 (20.0%)	8 (80.0%)	1.000
Cardiovascular medications	19 (27.9%)	49 (72.1%)	0.334
Radiotherapy	30 (25.0%)	90 (75.0%)	0.620
Chemotherapy			
Docetaxel	32 (27.1%)	86 (72.9%)	0.085
Taxanes	33 (25.2%)	98 (74.8%)	0.523
Pertuzumab	5 (19.2%)	21 (80.8%)	0.620
Anthracyclines			
Treatment without anthracyclines	5 (10.4%)	43 (89.6%)	
Doxorubicin	27 (34.6%)	51 (65.4%)	0.009***
Epirubicin	1 (10.0%)	9 (90.0%)	
Both Doxorubicin and Epirubicin	2 (20.0%)	8 (80.0%)	
Metastasis	13 (24.1%)	41 (75.9%)	1.000
Breast Side			
Left	23 (28.7%)	57 (71.3%)	0.173
Right	12 (18.2%)	54 (81.8%)	
Hormone receptor status			
ER – PR -	15 (25.0%)	45 (75.0%)	
ER + PR -	1 (10.0%)	9 (90.0%)	
PR + ER-	1 (50.0%)	1 (50.0%)	0.581
ER + PR +	18 (24.3%)	56 (75.7%)	
Menopausal status			
Pre-menopausal	26 (28.6%)	65 (71.4%)	0.112
Post-menopausal	9 (16.4%)	46 (83.6%)	
OCP	8 (28.6%)	20 (71.4%)	0.623

TIC: Trastuzumab-Induced Cardiotoxicity, BMI: Body Mass Index, AC: Doxorubicin plus Cyclophosphamide, FEC: 5-fluorouracil plus Epirubicin plus Cyclophosphamide, OCP: Oral Contraceptive, ER: Estrogen Receptor, PR: Progesterone Receptor, CAD: Coronary Artery Disease.

Table 3:
Incidence of Trastuzumab-induced cardiotoxicity and treatment discontinuation

	n (%)	Presence of HF Symptoms	Permanent Treatment Discontinuation	Temporary Treatment Discontinuation	Treatment Without Discontinuation
TIC	35 (23.97)	15 (42.85%)	1 (2.85 %)	29 (82.85 %)	5 (14.28 %)
LVEF decline by ≥ 10 %	33 (94.28)	15 (42.85%)	1 (2.85 %)	27 (77.14 %)	5 (14.28 %)
LVEF decline to < 50 %	22 (62.85)	13 (37.14 %)	1 (2.85 %)	19 (54.28 %)	2 (5.71 %)

TIC: Trastuzumab-Induced Cardiotoxicity,
LVEF: Left Ventricular Ejection Fraction,
HF: Heart Failure

Table 4:
Trastuzumab-induced cardiotoxicity associated with concurrent chemotherapeutic medications.

Number of patients and their percent within the treatment group are included.

		Cardiotoxicity	
		No	**Yes**
Docetaxel	**No**	25 (89.3%)	3 (10.7%)
	Yes	86 (72.9%)	32 (27.1%)
Paclitaxel	**No**	98 (75.4%)	32 (24.6%)
	Yes	13 (81.3%)	3 (18.8%)
Nab paclitaxel	**No**	101 (75.9%)	32 (24.1%)
	Yes	10 (76.9%)	3 (23.1%)
Tamoxifen	**No**	51 (76.1%)	16 (23.9%)
	Yes	60 (75.9%)	19 (24.1%)
Letrozole	**No**	101 (74.8%)	34 (25.2%)
	Yes	10 (90.9%)	1 (9.1%)
Exemestane	**No**	109 (75.7%)	35 (24.3%)
	Yes	2 (100.0%)	0 (0.0%)
Eribulin	**No**	109 (75.7%)	35 (24.3%)
	Yes	2 (100.0%)	0 (0.0%)
Vinorelbine	**No**	102 (76.1%)	32 (23.9%)
	Yes	9 (75.0%)	3 (25.0%)
Cyclophosphamide	**No**	109 (75.7%)	35 (24.3%)
	Yes	2 (100.0%)	0 (0.0%)
Liposomal Doxorubicin	**No**	111 (76.6%)	34 (23.4%)
	Yes	0 (0.0%)	1 (100.0%)
Capecitabine	**No**	109 (76.8%)	33 (23.2%)
	Yes	2 (50.0%)	2 (50.0%)
Lapitinib	**No**	108 (76.6%)	33 (23.4%)
	Yes	3 (60.0%)	2 (40.0%)
Pertuzumab	**No**	90 (75.0%)	30 (25.0%)
	Yes	21 (80.8%)	5 (19.2%)
Carboplatin	**No**	87 (73.7%)	31 (26.3%)
	Yes	24 (85.7%)	4 (14.3%)
Gemcitabine	**No**	95 (74.8%)	32 (25.2%)
	Yes	16 (84.2%)	3 (15.8%)

Figures

Figure 1:

Trastuzumab-induced cardiotoxicity associated with Beta Blockers, statins and ACE inhibitors

Number of patients is included on each bar.

ACE inhibitors: angiotensin converting enzyme inhibitors

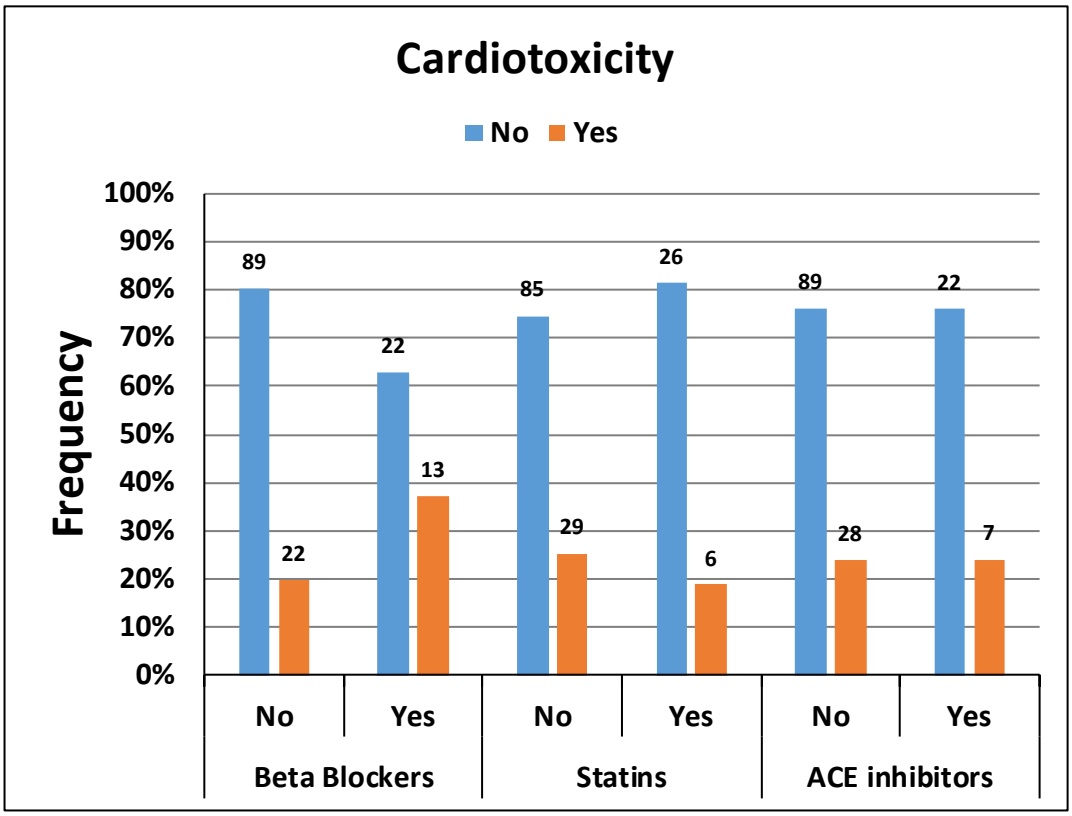
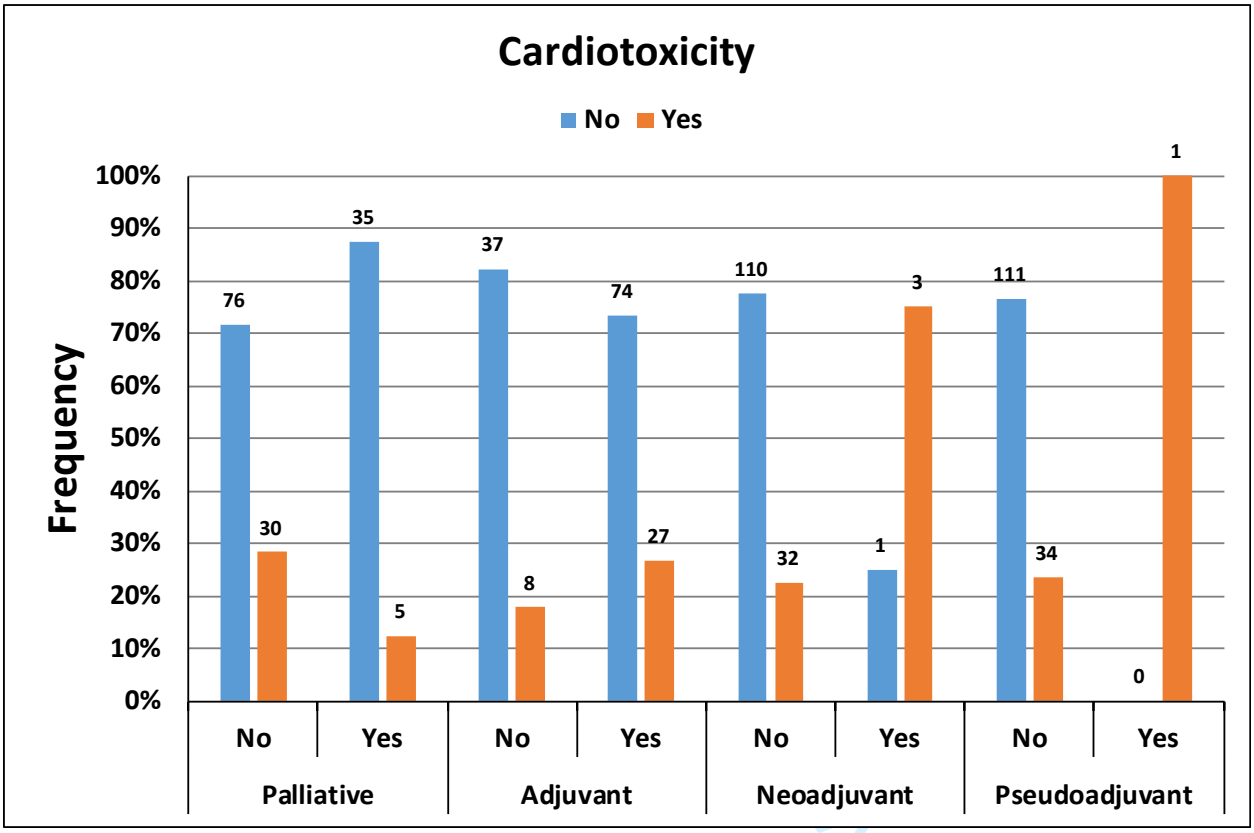


Figure 2:

Trastuzumab-induced cardiotoxicity associated with different treatment settings

Number of patients is included on each bar.



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