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Early Asymptomatic Decline in Left Ventricular Ejection Fraction in Adult Cancer Patients Receiving Trastuzumab

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ABSTRACT

Objective: To determine the frequency of Trastuzumab-induced early asymptomatic decline in left ventricular ejection fraction by serial Echocardiography and to identify various risk factors associated with cardio-toxicity.
Study Design: Quasi-experimental study.
Place and Duration of Study: Oncology Department, Combined Military Hospital, Lahore Pakistan, from Jan to Jun 2021.
Methodology: Patients who were started on Trastuzumab-based chemotherapy and had completed at least 600 mg subcutaneously every three weeks (amounting to 17 doses) in 1 year were enrolled. Surveillance modalities include Electrocardiography, chest X-ray and Echocardiography. These were done at baseline and after four cycles of chemotherapy. All patients were evaluated for the presence of the following risk factors: diabetes mellitus, hypertension, pre-existing coronary artery disease, and chest wall. Asymptomatic cardiac dysfunction was defined as an ejection fraction (EF) fall greater than 10% on follow-up echocardiography with minimum or no symptoms.
Results: The average baseline LVEF was 63.16±2.42 %, which decreased significantly to an average EF of 59.67±6.10%. In our study, 40 patients (66.7%) showed no decline in LVEF post-completion of chemotherapy. 6 patients (10.0%) showed an insignificant <10% decline in LVEF, and 14 patients (23.3%) showed significant >10% decline in LVEF. Frequency of decline in LVEF was observed in 20 out of 60 patients (33.33%), with 14 out of 60 patients (23%) having significant (i.e., ≥10%) decline in LVEF and 6 out of 10 patients (10%) having insignificant (i.e.,≤ 10%) decline in LVEF.
Conclusion: This entails regular monitoring for cardiac dysfunction by Echocardiography during Trastuzumab treatment.

Keywords: Cardiotoxicity, Echocardiographic monitoring, Trastuzumab.

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INTRODUCTION

Trastuzumab is one of the most potent anti-neoplastic agents widely used in managing breast carcinoma with HER2-positive oncogene.[1,2] Trastuzumab is a recombinant humanized monoclonal antibody that binds a family of extracellular growth factors, specifically human epidermal growth factor type-2 commonly referred to as HER2- Neu or ErbB2. HER2 is also physiologically expressed on myocytes; therefore, clinical use of Trastuzumab is associated with reversible cardiotoxicity, manifested as a reduced left ventricular ejection fraction.[3] This reduction in left ventricular systolic function is often demonstrated as signs and symptoms of heart failure in patients. Despite the reversible nature of cardiotoxicity, the development of advanced symptoms of cardiac disease often leads to discontinuing Trastuzumab as an anti-neoplastic agent.[4]

Trastuzumab-induced cardiotoxicity also warrants a careful evaluation of patients' risk factors before chemotherapy. Studies reveal age (>65 years), concomitant exposure to other chemotherapeutic agents, specifically anthracyclines, pre-existing cardiovascular disease, diabetes mellitus and obesity are the most important risk factors that predispose a patient to Trastuzumab-induced cardiotoxicity.[5,6]

Clinically significant side effects of Trastuzumab warrant screening for cardiac insufficiency before initiating treatment with Trastuzumab both clinically and by an imaging modality for calculating ejection fraction (EF). Clinical manifestations and electrocardiography are not sensitive and specific regarding labelling cardiotoxicity.[7] Endomyocardial biopsy is the most specific in detecting Trastuzumab-induced cardiomyopathy, but being an invasive procedure, it cannot be commonly employed. Another surveillance method is radionucleotide imaging, which has the advantage of being more sensitive but exposes the patient to ionizing radiation, which is not readily available; both factors limit its use.[8,9] Therefore, Echocardiography remains the most commonly used modality for detecting Trastuzumab-induced cardiotoxicity.

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The ACC (American College of Cardiology) recommends Echocardiography every three months during active treatment, while post-treatment surveillance can range between 1 and 5 years.[6] In our study, Echocardiography was conducted before initiation and after four cycles of chemotherapy to look for an early asymptomatic decline in ejection fraction.[10] Early detection of Trastuzumab-derived cardiotoxicity is important as it can prevent reversible and possibly irreversible effects on the cardiac function by early discontinuation of Trastuzumab and/or early implementation of cardio-protective therapies.

METHODOLOGY

The quasi-experimental study was conducted at the Oncology Department, Combined Military Hospital, Lahore Pakistan, from January to June 2021, with approval by the Institutional Ethical Committee (Reference number 283/2021). Non-probability consecutive sampling was employed. Sample size calculated by using the WHO sample size calculator, taking a 4.1% decrease in LVEF in patients receiving Transtuzumab.[3]

Inclusion Criteria: All recently diagnosed adult cancer patients of either gender, aged 18-65 years who were given Trastuzumab for the first time and had a left ventricular ejection fraction (LVEF) greater than or equal to 50% at baseline were included in the study.

Exclusion Criteria: Patients having congestive cardiac failure, patients with any valvular heart disease, and patients with Ejection Fraction less than 50% at baseline, were excluded.

A detailed history of pre-existing hypertension and diabetes mellitus was taken. Physical examination of the cardiovascular system was done at baseline and at each follow-up to rule out new onset valvular heart disease and congestive cardiac failure. Blood complete picture, 12-lead ECG, chest X-ray and Echocardiography were done at baseline and within three months after completion of chemotherapy. M-mode and modified Simpson's formula were used to calculate the Ejection fraction during Echocardiography.[11] It was ensured that the same physician performed both baseline and follow-up Echocardiography, taking the mean of three readings for each patient to minimize inter-observer and intra-observer variability. During follow-up echocardiography Subclinical cardiac dysfunction was defined as fall of ejection fraction >10%.

Statistical Package for Social Sciences (SPSS) version 26 was used for statistical analysis. Quantitative variables were expressed as Mean±SD and qualitative variables were expressed as frequency and percentages. Chi-square test was applied to explore the inferential statistics. The *p*-value ≤0.05 was considered as significant.

RESULTS

Sixty patients who completed a minimum of 600mg subcutaneous Trastuzumab every three weeks were enrolled in the study during the study period, amounting to 17 doses in one year for their cancer treatment. All the patients enrolled in the study received only Trastuzumab during their treatment course. Fifty-six female patients (93.3%) and four male patients (6.7%) were included in the study. The baseline characteristics of 60 patients are shown in Table-I.

Table-I: Baseline Characteristics of adult Cancer patients receiving Trastuzumab (n=60)

Characteristics	Mean(±SD)
Age(Years)	47.50±10.9 (Range: 10-69) years
Baseline LVEF (%)	63.16±2.42 (Range: 60-65)%

The average baseline LVEF was 63.16±2.42%, which decreased significantly to an average LVEF of 59.67±6.10%. Percentage reduction in LVEF % from baseline is shown in the Figure.

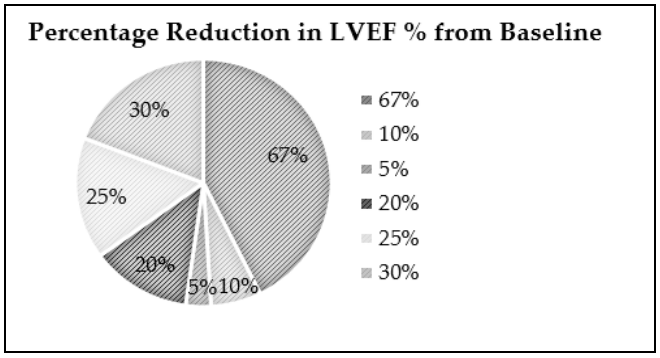

Figure: Percentage Reduction in LVEF % from Baseline (n=60)

In our study, 40 patients (66.7%) showed no decline in LVEF post-completion of chemotherapy. 6 patients (10.0%) showed an insignificant <10% decline in LVEF, and 14 patients (23.3%) showed significant >10% decline in LVEF. There was a statistically significant association of a decrease in ejection fraction with age, having a *p*-value of 0.003. All 100% of patients received Trastuzumab subcutaneously over 10 minutes. The link between various risk factors associated with a decline in ejection fraction was also studied. Of the 14 patients with a notable decline in LVEF after getting Trastuzumab-based chemotherapy, 10(16.6%) had hypertension. Interestingly, diabetes

mellitus was not identified as a risk factor for Trastuzumab-related cardiac toxicity in our study population. The association of change in ejection fraction (EF) with different risk factors in patients receiving Trastuzumab is shown in Table-III.

Table-II: Decline in ejection fraction with trastuzumab with respect to age (n=60)

		Ejection Fraction After Trastuzumab			*p*-value
		No Change (n=40)	<10% Decrease in EF (n=6)	≥10% Decrease in EF (n=14)	
Age (years)	25-49	20 (33.3%)	6 (15.0%)	12 (20.0%)	0.003
	50-75	20 (33.3%)	0	2 (3.3%)	

Table-III: Association of change in Ejection Fraction (EF) with different Risk Factors in Patients receiving Trastuzumab (n=60)

Risk factors		Ejection Fraction Reduction			*p*-value
		No change Ejection in Fraction (n=40)	<10% Reduction in EF (n=6)	≥10% Reduction in EF (n=14)	
Hyper-tension	No (n=48)	38 (63.3%)	6 (10%)	4 (6.6%)	<.001
	Yes (n=12)	2 (3.3%)	0	10 (16.6%)	
Diabetes Melltus	No (n=46)	32 (53.3%)	6 (10.0%)	8 (13.3%)	0.08
	Yes (n=14)	8 (13.3%)	0	6 (10%)	

DISCUSSION

Trastuzumab is given as a part of a combination chemotherapy regimen, and it primarily targets the human epidermal growth factor receptor two oncogene and significantly improves survival. Trastuzumab has become the standard of care in adjuvant and metastatic chemotherapeutic regimens.[11] Cardiotoxicity is frequent in patients receiving Trastuzumab (Trastuzumab) therapy, often referred to as Trastuzumab-related cardiac dysfunction (TRCD). TRCD is not dose-dependent and has multiple risk factors.[12] This study was aimed to determine Trastuzumab induced early asymptomatic decline in left ventricular ejection fraction and to identify risk factors associated with cardiotoxicity.

Our study shows that serial echocardiographic measurements can detect symptomatic and asymptomatic cardiac dysfunction in Trastuzumab patients. The frequency of decline in LVEF was 33.33% (20 out of 60 patients), with 23% (14 out of 60 patients) having significant (i.e.,≥10%) decline in LVEF and 10% (6 out of 60 patients) having insignificant (i.e.,≤ 10%) decline in LVEF. One study showed an incidence of TRCD at 35% in their study,[13] while another study found that 22% of patients developed TRCD.[14] In our study, all the patients were evaluated by Echocardiography before entry into the study, and cardiology consultation was taken before starting Trastuzumab. Other reasons could be comorbid conditions like hypertension and diabetes mellitus in our patients and the measurement method employed to determine LVEF. Some of the studies have used the index for measuring cardiac functions.[15]

Early detection of cardiac dysfunction in patients receiving Trastuzumab has important clinical implications. Recovery is usually possible by temporarily holding Trastuzumab therapy and starting cardiac therapy with a beta blocker and/or ACE inhibitor. After left ventricular systolic function recovers, Trastuzumab can be resumed.[16] It may be feasible to continue Trastuzumab despite mild cardiotoxicity in the setting of a cardio-oncology clinic, where ACE inhibitors and beta-blockers are administered to patients with EF 40% and the lower limit of normal or if EF falls to 15% from the baseline. Approximately 10% of patients may develop moderate to severe heart failure using this approach.[17]

This study was unique as it was prospective in design and used Echocardiography to measure ejection fraction, which is widely available. Most of the studies we found were retrospective and dependent on patient records. Our study was limited by its sample size, and cardiac function should have also been evaluated by MUGA scan. Earlier studies have shown that MUGA scan is more reliable than Echocardiography. Future studies should focus on the frequency of cardiac evaluations and address the issue of the most cost-effective method of cardiac function assessment. A longer follow-up of the patients in which early decline in cardiac function is recorded is also warranted. The paucity of literature about the long-term complications of Trastuzumab is perhaps explained by the physicians' belief that it is reversible, and perhaps the treating physicians focus more on the immediate morbidity and mortality of cancer. With the increasing number of patients surviving after cancer therapy, there is an emergent need for future studies in this direction.[18]

Interestingly, diabetes mellitus could not be identified as a risk factor for Trastuzumab induced cardiotoxicity in our study population. This could be due to the small sample size of our study. Upcoming cardiac safety data in elderly patients receiving Trastuzumab-based therapy within prospective clinical trials are awaited with great expectation. Similarly, assessing Troponin-I level might be useful to establish the diagnosis and prognosis of Trastuzumab-related cardiotoxicity.

CONCLUSION

Treatment with Trastuzumab is associated with frequent reversible cardiotoxicity, which can be projected by the alterations that occur in ejection fraction pre-treatment and after taking Trastuzumab. Known cases of coronary artery disease and hypertension have been recognized as risk factors for developing cardiac dysfunction using Trastuzumab. Frequent monitoring of the patients with Echocardiography is therefore essential for all patients receiving Trastuzumab for carcinoma breast. Holding Trastuzumab and initiating cardiac therapy usually results in therapy.

Conflict of Interest: None.

Author's Contribution

Following authors have made substantial contributions to the manuscript as under:

MZ: & FM: Conception, study design, drafting the manuscript, approval of the final version to be published.

ZG: & MK: Data acquisition, data analysis, data interpretation, critical review, approval of the final version to be published.

AA: & MUS: Critical review, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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