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Original Research Article

A Hospital Based Prospective Assessment of Cardiotoxicity Profile of Breast Cancer Patients Receiving Trastuzumab in Adjuvant and Maintenance

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Abstract

Aim: The aim of the present study was to assess the cardiotoxicity profile of our patients receiving trastuzumab in adjuvant and maintenance settings in breast cancer patients.

Methods: The present study was a prospective, conducted in Department of Medical Oncology, IGIMS, Patna, Bihar, India over a period of 2 years. 50 patients were included in the study.

Results: The median age of presentation was 46 years (range: 24 to70 years). All patients were of the female sex. Majority of the patients (56%) belonged to the age group of 41–50 years. Majority of the patients had no known comorbidities such as hypertension (HTN) or diabetes mellitus (DM). Out of 50 HER2 new‐positive patients, 21 cases (42%) were triple positive, 28 (56%) were hormone receptor (HR) negative, while 1 (2%) were estrogen receptor (ER) positive but progesterone receptor (PR) negative. According to the stage‐wise distribution, majority of patients (n = 28; 56%) presented at Stage IIB followed by Stage IIA (n = 19; 38%). In the present study, 26 patients received prior anthracycline‐based chemotherapy while 24 patients received nonanthracycline‐based chemotherapy. During treatment, a drop of >10% was considered a clinically significant drop and treatment was temporarily halted till the cardiac function was restored. Adequate cardiology consultation and intervention was done. Over 1‐year period of trastuzumab therapy, all the patients experienced some kind of drop in LVEF and a significant drop in LVEF (>10%) was observed in 17 (34%) out of 50 patients.

Conclusion: Identifying women at risk of developing trastuzumab related cardiac dysfunction when starting adjuvant trastuzumab treatment continued to be an ongoing challenge. The discovery of trastuzumab has changed the paradigm of treatment for the HER2‐expressed breast cancer patients who otherwise have an aggressive tumor biology.

Keywords: Breast Cancer, Cardiotoxicity, Echocardiography, Prior Anthracycline‐Based Chemotherapy, Trastuzumab.

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]

High blood pressure (HBP), age over 50 years, increased body mass index (BMI), exposure to anthracyclines and borderline baseline left ventricular ejection fraction (LVEF) are known risk factors for trastuzumab-related cardiotoxicity, derived from randomized adjuvant trials. [3] Regarding the other possible predictive factors for trastuzumab-related cardiotoxicity, such as N-terminal pro-brain natriuretic peptide (NT-proBNP) [4-6] and some echocardiographic measurements, like left ventricular end-systolic volume (LVESV), peak systolic wave velocity at septal mitral position in tissue Doppler imaging (Sm wave), early diastolic wave velocity at septal mitral position in tissue Doppler imaging (Em wave), left atrial area (LA) and E to A wave velocity ratio in mitral inflow pulse Doppler (E/A), either evidence is weak or have not been studied extensively. [7-10]

Adjuvant trastuzumab significantly reduces mortality and the risk of relapse in human epidermal growth factor receptor-2 (HER-2) positive breast cancer patients.11-13 However, trastuzumab therapy is associated with significant cardiotoxicity and trastuzumab-related cardiac dysfunction has been recognized as an important side effect and the main reason for premature therapy discontinuation. [11,14] Cardiac dysfunction with trastuzumab is often asymptomatic but can be symptomatic as well and the cardiotoxicity has been found to be aggravated with the prior use of chemotherapeutic agents such as anthracyclines. Previously published literatures showed that cancer therapy‐related cardiac dysfunctions range from 9% to 26% after treatment with doxorubicin, 13%–17% with trastuzumab, and 27%–34% with combination therapies. [15,16] The concurrent use of doxorubicin (anthracycline based) chemotherapy causes increased oxidative stress via mitochondrial and iron‐dependent generation of superoxide which is then transformed into hydrogen peroxide and peroxynitrite. These reactive oxygen and nitrogen species aggravate the imbalance between pro‐survival and pro‐apoptotic signaling leading to cardiac cell death. [17]

The aim of the present study was to assess the cardiotoxicity profile of our patients receiving trastuzumab in adjuvant and maintenance settings in breast cancer patients. [18]

Materials and Methods

The present study was a prospective, conducted in Department of Medical Oncology, IGIMS, Patna, Bihar, India over a period of 2 years. 90 HER2‐positive breast cancer patients were screened for eligibility, of which 25 patients presented with metastatic disease and hence excluded from the study. From 65 remaining cases, 4 patients had cardiac dysfunction at baseline, 6 had received trastuzumab within 6 months, and 5 patients defaulted treatment, and hence,

these 15 cases were excluded. Therefore, a total of 50 HER2‑positive breast cancer patients fulfilled the inclusion and exclusion criteria and enrolled in the study for analysis.

The HER2‑positive breast cancer patients who were planned to receive trastuzumab along with chemotherapy in adjuvant setting followed by trastuzumab alone in maintenance setting were included in the study analysis. The study evaluates the trastuzumab‑induced decline in cardiac function. The patients with Eastern Cooperative Oncology Group Performance Status (PS) >2, those with baseline left ventricular ejection fraction (LVEF) <55% on echocardiography or on previous cardiac medications, those having metastatic disease, and other patients who received prior trastuzumab‑based therapy were excluded from the study enrollment.

The details of patient characteristics including demographic, pathological, and clinical profiles and imaging findings were recorded. Immunohistochemistry (IHC) finding of 3+ was considered HER2 positive. In case of equivocal findings on IHC, fluorescence in situ hybridization analysis was done for confirmation of HER2 positivity. A proper clinical staging was done for all the patients as per the AJCC manual 8th Edition. Trastuzumab was given at a dose of 8 mg/kg body weight as a loading dose in the first cycle followed by 6 mg/kg body weight in the subsequent cycles at every 3 weekly intervals.

The various chemotherapy regimens that were followed, both in the adjuvant setting were:

1. AC regimen consisted of Adriamycin 60 mg/m2 plus cyclophosphamide 600 mg/m2.
2. EC regimen consisted of epirubicin 90–100 mg/m2 plus cyclophosphamide 600 mg/m2.
3. D+T regimen consisted of docetaxel at 100 mg/m2 plus trastuzumab.
4. P+T regimen consisted of paclitaxel 175 mg/m2 plus trastuzumab.
5. TCH regimen consisted of docetaxel 75 mg/m2 plus carboplatin area under curve 5 plus trastuzumab. All the regimens were given intravenously on a day 1 basis at 3 weekly intervals and they were followed with maintenance trastuzumab at 6 mg/kg body weight 3 weekly up to 16 cycles (1 year).

Patients were evaluated for cardiotoxicity by history and clinical examination (looking for overt signs of heart failure [HF]) and echocardiography imaging evaluation. Echocardiography was done at the baseline, prior to initiation of trastuzumab therapy and at regular intervals of every 3 cycles after the start of trastuzumab up till the completion of one year of treatment i.e. 16 cycles of Trastuzumab based treatment. LVEF value was determined on echocardiography, and the lower limit of normal value was 55%. A significant fall of ejection fraction was defined as a fall of LVEF >10% from the lower limit of normal range.[8] The treatment was interrupted for such patients when the drop in LVEF was found to be >10% and was resumed on correction of the same. The drop in LVEF was determined for all the patients. Subgroup analysis for drop in LVEF was done for those patients who received prior anthracycline‑based chemotherapy and for those who did not receive prior anthracycline.

Statistical analysis

The data collected were entered into Microsoft Excel sheet and analyzed using SPSS statistics software for Windows, version 23 (IBM Corp., Armonk, New York, USA). Categorical data were represented in the form of frequencies and proportions. The difference in drop in

LVEF between the two groups was analyzed using Chi‑square test. $P < 0.05$ was considered statistically significant.

Results

Table 1: Basic characteristics of the patient profile

Variables	Values, n (%)
Age groups (years)	
21-30	2 (4)
31-40	12 (24)
41-50	28 (56)
51-60	6 (12)
>60	2 (4)
Gender	
Male	0
Female	50 (100)
ECOG PS	
1	44 (88)
2	6 (12)
Comorbidities	
Hypertension only	10 (20)
Diabetes Mellitus only	2 (4)
Both	0
None	38 (76)
Receptor status	
Triple positive	21 (42)
Hormone receptor negative	28 (56)
Hormone receptor positive	1 (2)
Stage of the disease	
Stage IIA	19 (38)
Stage IIB	28 (56)
Stage IIIA	3 (6)
Prior anthracycline‑based chemotherapy	
Received	26 (52)
Not received	24 (48)

The median age of presentation was 46 years (range: 24 to70 years). All patients were of the female sex. Majority of the patients (56%) belonged to the age group of 41–50 years. Majority of the patients had no known comorbidities such as hypertension (HTN) or diabetes mellitus (DM). Out of 50 HER2 neu‑positive patients, 21 cases (42%) were triple positive, 28 (56%) were hormone receptor (HR) negative, while 1 (2%) were estrogen receptor (ER) positive but progesterone receptor (PR) negative. According to the stage‑wise distribution, majority of patients (n = 28; 56%) presented at Stage IIB followed by Stage IIA (n = 19; 38%). In the present study, 26 patients received prior anthracycline‑based chemotherapy while 24 patients received nonanthracyclin e‑based chemotherapy.

Table 2: Left ventricular ejection fraction drop after every 3 cycles of trastuzumab

Parameters	3rd cycle	6th cycle	9th cycle	12th cycle	16th cycle
Prior anthracycline‑based CT (n=26)					
Drop in LVEF, n (%)					

≤10	0	0	2	5	6
>10	0	2	3	6	2
No Prior anthracycline‑based CT (n=24)					
Drop in LVEF, n (%)					
≤10	0	0	2	8	10
>10	0	0	1	1	2

During treatment, a drop of >10% was considered a clinically significant drop and treatment was temporarily halted till the cardiac function was restored. Adequate cardiology consultation and intervention was done. Over 1‑year period of trastuzumab therapy, all the patients experienced some kind of drop in LVEF and a significant drop in LVEF (>10%) was observed in 17 (34%) out of 50 patients.

Table 3: Comparison of drop in left ventricular ejection fraction between prior anthracycline versus no prior anthracycline groups

Drop in LVEF (%)	Prior anthracycline‑based chemotherapy (n=26), n (%)	Nonanthracycline chemotherapy (n=24), n (%)	P
≤10	13 (50)	20 (83.34)	0.0120
>10	13 (50)	4 (16.66)	

During subgroup analysis, when a drop in LVEF was evaluated between types of chemotherapy, it was found that 50% of patients (13 out of 26) who received prior anthracycline‑based chemotherapy and 16.66% of patients (4 out of 24) who did not receive prior anthracycline experienced >10% drop in LVEF. The Chi‑square test was applied to compare the difference between these two groups and found to be statistically significant.

Discussion

Breast cancer is the most common cancer among women worldwide and >1 million new cases are diagnosed yearly. [19] The overexpression of human epidermal growth factor receptor‑2 (HER2) is seen in 20%–25% of breast cancers. HER2 overexpression has been found to be associated with aggressive growth and poor prognosis. [20] Trastuzumab is a humanized monoclonal antibody which acts against the extracellular domain of HER2, targeting HER2 overexpressing tumors.

The median age of presentation was 46 years (range: 24 to70 years). All patients were of the female sex. Majority of the patients (56%) belonged to the age group of 41–50 years. Cardinale et al. [21] in their study on HER2‑positive breast cancer patients found the mean of presentation of 50 ± 10 years. Out of 50 HER2 neu‑positive patients, 21 cases (42%) were triple positive, 28 (56%) were hormone receptor (HR) negative, while 1 (2%) were estrogen receptor (ER) positive but progesterone receptor (PR) negative. According to the stage‑wise distribution, majority of patients (n = 28; 56%) presented at Stage IIB followed by Stage IIA (n = 19; 38%). In the present study, 26 patients received prior anthracycline‑based chemotherapy while 24 patients received nonanthracycline‑based chemotherapy.

During treatment, a drop of >10% was considered a clinically significant drop and treatment was temporarily halted till the cardiac function was restored. Adequate cardiology consultation and intervention was done. Over 1‑year period of trastuzumab therapy, all the patients experienced some kind of drop in LVEF

and a significant drop in LVEF (>10%) was observed in 17 (34%) out of 50 patients. Several pivotal adjuvant clinical trials have been reported symptomatic congestive HF rates which range from 0.8% to 5.1% and decreased LVEF (>10%) rates which range from 3.5% to 19%. [22-25] Aggarwal et al. [26] in a study, reported >10% drop in LVEF in 4.6% of patients. Due to poor prognosis of HER2‐positive breast cancer patients, the trastuzumab‐induced cardiotoxicity should be weighed against its potential clinical benefit. Although there are improved outcomes with the use of trastuzumab, cardiac toxicity is an important concern for medical oncologists, cardiologists and patients. [27]

During subgroup analysis, when a drop in LVEF was evaluated between types of chemotherapy, it was found that 50% of patients (13 out of 26) who received prior anthracycline‐based chemotherapy and 16.66% of patients (4 out of 24) who did not receive prior anthracycline experienced >10% drop in LVEF. The Chi‐square test was applied to compare the difference between these two groups and found to be statistically significant. Aggarwal et al.[26] similarly demonstrated a mean drop of >10% in LVEF profiles in 4.6% of patients which developed over after a mean of 6 months after starting therapy with trastuzumab.

Conclusion

Identifying women at risk of developing trastuzumab related cardiac dysfunction when starting adjuvant trastuzumab treatment continued to be an ongoing challenge. The discovery of trastuzumab has changed the paradigm of treatment for the HER2‐expressed breast cancer patients who otherwise have an aggressive tumor biology. Clinical deterioration of the cardiac function or a drop in LVEF by >10% may lead to interruption in the treatment till stabilization and improvement of the cardiac function.

It is hence very important to keep a keen eye and look for clinical as well as laboratory parameters to determine any deterioration in cardiac functioning of patients on trastuzumab, especially in those who have a prior history of anthracycline‐based chemotherapy.

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