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Breast Cancer

Trastuzumab-Related Cardiotoxicity in Adjuvant Setting: A Real-World Scenario

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Abstract

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Trastuzumab, a humanized monoclonal antibody, significantly improves outcomes in *HER*2-neu positive breast cancer. The incidence of cardiotoxicity with trastuzumab is approximately 8 to 10%. This study was designed to analyze the incidence and risk factors associated with trastuzumab-related cardiotoxicity in real-world settings. This was a single institutional retrospective analysis of the incidence of trastuzumab-related cardiotoxicity in nonmetastatic *HER*2-positive, invasive breast cancer from January 2013 to December 2018. Trastuzumab-related cardiotoxicity was defined as symptomatic heart failure or asymptomatic decline in left ventricular ejection fraction (LVEF) by more than or equal to 10% or LVEF less than 50%. Risk factors analyzed were higher body mass index ($\geq$30 kg/m^2), history of diabetes, hypertension, cardiac disease, left-sided radiotherapy (RT), and prior exposure to anthracyclines. Out of the 246 patients diagnosed with early stage *HER*2-positive breast cancer, 117 (47.5%) received trastuzumab and constituted the study population. Trastuzumab-related cardiotoxicity was seen in a total of 16 (13.6%) patients. Eleven (9.4%) patients had an asymptomatic decline, while symptomatic LV dysfunction was seen in five (4.2%) patients. The median baseline ejection fraction was 65% (range, 56–72). The median time to development of cardiotoxicity was 18.5 weeks (range, 3–52) and the median trastuzumab cycle for cardiotoxicity was 6 (range, 2–16). Ten (62.5%) patients were rechallenged with trastuzumab following which one patient developed an asymptomatic decline in ejection fraction and one patient developed symptomatic heart failure. Cardiac-related mortality was seen in one (0.85%) patient. Left-sided RT to chest ($p = 0.012$) and presence of more than or equal to two risk factors ($p = 0.01$) had significant impact on incidence of cardiotoxicity. Approximately 14% developed trastuzumab-related cardiotoxicity that was slightly higher compared with that seen in clinical trials. Left-sided RT to chest and presence of two or more risk factors had significant impact on development of cardiotoxicity.

Keywords

- *HER*2
- trastuzumab
- early breast cancer
- cardiotoxicity

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Introduction

Breast cancer is a heterogenous disease with approximately 15 to 20% having an overexpression of *HER*2/neu (human epidermal growth factor receptor) protein, mostly driven by gene amplification. Tumors with *HER*2 protein overexpression are known to be aggressive, rapidly growing with early lymph nodal and distant metastasis, early relapse, and lower survival rates. Trastuzumab, a humanized monoclonal antibody, binds to the dimerization subdomain IV of the extracellular domain of the *HER*2 receptor. Evidence supports antibody-dependent cell-mediated cytotoxicity as the major mechanism of action of trastuzumab.[1] Other mechanisms include inhibition of *HER*2 homodimers and heterodimers, inhibition of angiogenesis, and blocking DNA damage repair.

*HER*2 signaling plays an important role in development, survival, and stress adaptation of cardiomyocytes. Trastuzumab, by inhibiting *HER*2, causes cardiac damage by suppressing myofilament protein synthesis, inhibiting cell survival, upregulating protein degradation and inhibition of autophagy, leading to production of reactive oxygen species in cardiomyocytes.[2] Several risk factors including prior anthracycline therapy, older age, hypertension, obesity, and history of cardiac dysfunction predispose to this undesirable event. This was a retrospective study of the incidence of trastuzumab-related cardiotoxicity in early breast cancer in real-world scenario and the risk factors predisposing to this condition.

Materials and Methods

Data Collection

This study is a retrospective, observational study. Data of patients with breast cancer who received trastuzumab in the adjuvant setting between January 2013 and December 2018 was analyzed. Patients were included in the study if they had received at least one dose of trastuzumab and had periodic left ventricular ejection fraction (LVEF) assessments at well-defined time points during treatment. The patients were treated as per clinical guidelines, including surgery, chemotherapy, radiotherapy (RT) (if indicated), and endocrine therapy (in hormone receptor positive disease). Trastuzumab was administered at a loading dose of 8 mg/kg body weight intravenously once followed by maintenance dose of 6 mg/kg body weight every 3 weeks for 1 year. The study protocol was reviewed and approved by the institutional review board. Baseline characteristics including age, performance status, menopausal status, smoking habits, prior cardiac disease (congestive heart failure, coronary artery disease, wall motion abnormalities, angina pectoris, valvular disease, arrythmias or cardiac intervention for any other reason), hypertension, diabetes mellitus, and body mass index (BMI) were documented. Disease and treatment details including breast cancer sidedness, stage, Her2/neu status (determined by either *HER*2 immunohistochemistry (IHC) score of 3+ or fluorescent *in situ* hybridization [FISH]) amplification), type of surgery, chemotherapy regimen, cumulative anthracycline dose, trastuzumab dosage and number of cycles, local radiation treatment portals, and dose-fractionation were collected. Cardiac evaluation included symptom and physical evaluation at each trastuzumab cycle and assessment of LVEF by two-dimensional (2D) echocardiography, at baseline and 3rd, 6th, 9th, and 12th month during trastuzumab cycles.

Trastuzumab-related cardiotoxicity was defined as symptomatic heart failure or asymptomatic decline in LVEF by more than or equal to 10% from baseline or LVEF less than 50%.[3] Trastuzumab was discontinued if patients develop symptomatic heart failure or recovery time was more than 4 weeks. Risk factors analyzed included age more than or equal to 50 years, BMI more than or equal to 30 kg/m^2, hypertension, diabetes, cardiac disease, prior anthracycline exposure, and left-sided RT.

Statistics

Continuous variables were described as median with range and discrete variables were expressed as numbers and/or percentages. Risk factors associated with cardiotoxicity were analyzed using the chi-squared test. A *p*-value of less than 0.05 was considered to be statistically significant. SSPS version 25 (SSPS, Chicago, Illinois, United States) was used for statistical analysis.

Results

Between 2013 and 2018, a total 1,535 cases of breast cancer were registered. Of these, 246 were diagnosed as *HER*2 positive nonmetastatic breast cancer. Among these, 117 patients received trastuzumab and were included in the study.

Baseline Characteristics

The median age at presentation was 51 years (range, 28–72). Ninety-three patients (79%) were postmenopausal. Twenty-six (22%) patients had a BMI more than or equal to30 kg/m^2. History of cardiac disease, hypertension, and diabetes mellitus was present in 3 (3%), 39 (33%), and 24 (20%) patients. None of the patients were smokers. Median baseline ejection fraction (before trastuzumab treatment) was 65% (range, 56–72).

Disease and Treatment Characteristics

Majority (50.5%) of the patients had stage III disease. *HER*2 status was ascertained by IHC in 92 (79%) with additional 25 (21%) requiring confirmation by FISH. Adjuvant chemotherapy was anthracycline based in 78 (67%) and taxane based in 39 (33%) patients. Sixty-two (53%) patients were treated with radiation with left-sided RT received by 32 (27%) patients. The baseline characteristics and treatment details of patients receiving trastuzumab are shown in ►Table 1.

Trastuzumab-Related Cardiotoxicity

Trastuzumab-related cardiotoxicity was observed in 16 (13.7%) patients. Eleven (69%) patients had an asymptomatic decline in LVEF, while five (31%) patients had symptomatic LV dysfunction. The median age of patients who developed cardiotoxicity was 55.5 years (range, 42–64). Majority of them were postmenopausal (94%). Cardiovascular disease,

Table 1 Baseline and treatment characteristics of breast cancer patients receiving trastuzumab

Characteristic	Total ($n = 117$)	Cardiotoxicity ($n = 16$)
Median age at presentation in years	51 (range, 28–72)	55.5 (range, 42–64)
Menopause status		
Premenopausal	24 (21%)	1 (6%)
Postmenopausal	93 (79%)	15 (94%)
BMI $\geq$30 kg/m^2	26 (22%)	2 (12.5%)
Known cardiac disease	3 (3%)	1 (6%)
Hypertension	39 (33%)	8 (50%)
Diabetes mellitus	24 (20%)	3 (18.6%)
Median baseline LVEF (range)	65% (range, 56–72)	65.5% (range,56–72)
Stage		
Stage I	6 (5.2%)	1 (6%)
Stage II	52 (44.3%)	5 (32%)
Stage III	59 (50.5%)	10 (62%)
Adjuvant chemotherapy		
Anthracycline based	78 (67%)	13 (81.2%)
Taxane based	39 (33%)	3 (18.8%)
Radiotherapy		
Left side	32 (27%)	9 (56%)
Right side	30 (26%)	4 (25%)

Abbreviations: BMI, body mass index; LVEF, left ventricular ejection fraction.

Table 2 Risk factors in relation to TRC

Risk factor	TRC present	TRC absent	*p*-Value
Age			
$\geq$ 50	12	59	0.2
$<$ 50	4	42	
BMI			0.5
$\geq$ 30	2	24	
$<$ 30	14	77	
History of diabetes			0.85
Yes	3	21	
No	13	80	
History of hypertension			0.2
Yes	8	31	
No	8	70	
Cardiac disease			0.87
Yes	1	2	
No	15	99	
Left-side radiotherapy			0.012
Yes	9	23	
No	7	78	
Prior anthracycline			0.29
Yes	13	65	
No	3	36	

Abbreviations: BMI, body mass index; TRC, trastuzumab-related cardiotoxicity.

hypertension, and diabetes was present in one (6%), eight (50%), and three (18.6%) patients, respectively. BMI of more than or equal to 30 kg/m^2 was seen in two (12.5%) patients. Majority of patients (94%) underwent Modified Radical Mastectomy (MRM). Chemotherapy was anthracycline based in 13 (81.2%) and taxane based in 3 (18.8%) patients. Radiation was received by 13 (81%) patients, with left-sided RT in 9 (56%) and right-sided in 4 (25%) patients. The median time to develop cardiotoxicity was 18.5 weeks (range, 3–52). Median trastuzumab cycle at the time of cardiotoxicity was 6 (range, 2–16). Cardiovascular medications were prescribed in 10 (63%) patients. Ten (63%) patients were rechallenged with trastuzumab after the recovery following which two (20%) patients redeveloped cardiotoxicity (1 asymptomatic and 1 symptomatic) and discontinued the drug permanently. The rate of discontinuation of trastuzumab due to cardiotoxicity was 6.8%. One patient had sudden death at home that was presumed to be sudden cardiac death and a detailed analysis and cause of death were not available.

Risk Factors and Trastuzumab-Related Cardiotoxicity

Among the potential risk factors analyzed, only left-sided RT ($p = 0.012$) was significantly associated with trastuzumab-related cardiotoxicity. There was no significant relationship between cardiotoxicity and other risk factors such as age more than 50 years, BMI more than or equal to 30 kg/m^2, hypertension, diabetes, cardiac disease, and prior anthracycline exposure. However, presence of two or more of the above risk factors (15 out of 16 patients) was found to have a significant impact on trastuzumab-related cardiotoxicity ($p = 0.01$). Risk factors in relation to trastuzumab-related cardiotoxicity are shown in ►Table 2.

Discussion

Although adjuvant trastuzumab has provided substantial benefit in HER2 positive breast cancer, associated cardiovascular toxicity is a cause of concern. Nonuniform definition of cardiotoxicity in various clinical trials and stringent selection criteria with inclusion of patients who were younger and with fewer cardiovascular comorbidities resulted in reporting of lower rates of cardiotoxicity compared with that in real-world setting. Furthermore, in most of these trials greater emphasis was laid on detecting severe symptomatic cardiac events, resulting in underappreciation of more frequent and less severe forms of cardiotoxicity.

Table 3 Reported rates of TRC in various studies

Characteristic	NSABP B-31 and N9831[6]	BCIRG 006[7]	HERA[3]	Wadhwa et al[3]	Tang et al[4]	Present study
% of patients with LVEF decline $\geq$ 10%	14.2	18.6	7	20.4	16.9	9.4
% of patients with symptomatic TRC	4	2	0.6	3.3	4.4	4.3

Abbreviations: LVEF, left ventricular ejection fraction; TRC, trastuzumab-related cardiotoxicity.

Reported rates of cardiotoxicity have been in range of 5.7 to 35.4% in randomized trials and 8.3 to 43.6% in real-world settings. In this study, the incidence of cardiotoxicity was 13.7% that is well within the range reported in literature. Asymptomatic decline in LVEF was observed in 9.4%, while symptomatic heart failure was documented in 4.3%. Rate of symptomatic heart failure has ranged from 4.2 to 17% in clinical trials. In a retrospective study by Wadhwa et al[4] comprising predominantly Caucasian population (92%), 20.4% had asymptomatic, while 3.3% had symptomatic LV dysfunction. Rates of asymptomatic and symptomatic LV dysfunction were 16.9 and 4.4% in a Canadian study by Tang et al.[5] ►**Table 3** shows reported rates of trastuzumab-related cardiotoxicity in various studies.

With regard to timing of cardiotoxicity, it appears that patients are most vulnerable in the first 6 months of trastuzumab therapy. The median time to develop cardiotoxicity in this study was 18.5 weeks (range, 3–52). SCHOLAR, a phase 1 study by Leong et al,[8] also reported cardiotoxicity occurring within 6 months in majority of the patients. Based on this observation, a few studies advocate focusing LVEF monitoring in the first 6 months and deescalating later as a cost-effective approach in resource limited settings.

Owing to the reversible nature of trastuzumab-related cardiac dysfunction, a question that arises in clinical context is whether trastuzumab can be safely reinitiated in such patients following recovery. In the North Central Cancer Treatment Group N9831 adjuvant breast cancer trial (NCCTG) trial, 50% of the patients who had developed cardiac dysfunction were restarted on trastuzmab.[9] In this study, 10 out of 16 (62.5%) patients were restarted on trastuzumab. LV dysfunction recurred in two (20%) of these patients. Although trastuzumab rechallenge appears to be fairly well tolerated in majority of patients, further research is needed to identify patients in whom it can be safely advised. In this study, trastuzumab was permanently discontinued in 6.8% due to cardiotoxicity. This is in agreement with the reported trastuzumab discontinuation rates ranging between 8.5 and 31.4% in clinical trials and 2.0 to 14.6% in community practice.

In this study, left-side irradiation (9 out of 16 patients) was significantly associated with cardiotoxicity ($p = 0.012$). An objective evidence comes from a study by Cao et al[10] which demonstrated that in left-sided patients, the dose-volume parameters of the heart and left ventricle were significantly higher in those with trastuzumab-related cardiotoxicity ($p < 0.05$). In this study, small sample size of subgroups limited the statistical power to decipher meaningful associations between other traditional risk factors and cardiotoxicity due to trastuzumab. However, presence of 2 or more cardiac risk factors predicted increased risk of cardiotoxicity ($p = 0.01$). As the effects of these variables in causing cardiotoxicty seem to be additive, lifestyle modifications and optimized medical management of patients with cardiovascular risk factors can minimize such events during trastuzumab treatment.

There were several limitations in this study. Ejection fraction assessment was done only by 2D echocardiography that is less reproducible and more prone to interreader variation. Biomarker testing including B-type natriuretic peptide and serum troponin was not preformed. Due to retrospective nature and limited data on cardiac follow-up of these patients, long-term toxicities of trastuzumab could not be ascertained.

Conclusions

The risk of cardiotoxicity appears to be modest in this real-world study. With majority of the patients experiencing only asymptomatic declines and predominantly reversible episodes, concerns for cardiotoxicity should reinforce more vigilant cardiac monitoring and not undermine this oncologic intervention with a substantial disease-free and overall survival benefit.

Funding

None.

Conflict of Interest

None declared.

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