Trastuzumab associated cardiac toxicity: who is at risk in Saudi Arabia? A single institution study

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Abstract

Purpose: There is a growing concern about the long-term effect of trastuzumab-induced cardiotoxicity (TIC). Therefore, we retrospectively assessed the incidence of TIC and heart failure (HF) and tried to identify possible risk factors among a group of Saudi breast cancer (BC) patients.

Methods: This retrospective cohort study was conducted to review all Her2 + BC patients treated at KAMC, Riyadh KSA, with trastuzumab in the adjuvant and metastatic settings between 2003 and 2012. Of 150 patients, 104 were eligible with good quality echocardiogram and base line LVEF > 55%. Cardiac function assessment was repeated every 3 months by echocardiogram thereafter.

Results: 104 Her2 positive breast cancer patients were eligible for analysis, with median age of 49 years and range (29->78 y). A significant decline in LVEF was observed in 16 patients (15.38%) at a mean exposure period of 15 months. On multivariate analysis a significant difference in LVEF decline was reported between patients diagnosed with hypercholesterolemia (64.71%) compared to (6.8%) in patients with normal cholesterol level (p-value 0.0001) as well as between patient who has been exposed to Anthracycline chemotherapy (p v-value 1.0435). Diabetes was a significant risk factor for TIC on univariate analysis but this was not confirmed on multivariate analysis.

Conclusion: Given the limitations of this retrospective review, the results showed significant higher prevalence of TIC among Her2 + BC Saudi patients. The study highlighted significant correlation between hyperlipidemia and previous exposure to Anthracycline with development of TIC constituting a high risk group patients who may need to be closely monitored for cardio toxicity.

Introduction

Breast cancer is the most common cancer among Saudi females, comprising 27.7% of all malignancies (13). Approximately 20 to 30% of all breast cancers overexpress human epidermal growth factor receptor 2 (Her2) (1). A variant of the disease associated with aggressive course and poor prognosis with a high risk of recurrence and metastasis (2). Trastuzumab, a monoclonal antibody targeting Her2 has led to a significant breakthrough in the treatment of breast cancer that over-expresses Erb-2 receptors, therefore, partnering trastuzumab with chemotherapy have improved the response rate, time to disease progression, and overall survival. At present, trastuzumab is considered part of the standard therapy for both advanced and early her2 positive breast cancer (3). Its use, however was associated with an unexpectedly high incidence of cardio toxicity usually occurring as asymptomatic LVEF reduction of >10% or overt heart failure (HF).

The risk factors for trastuzumab-induced cardio toxicity (TIC) have not been clearly defined. Moreover, the long-term impact of trastuzumab-related transient LVEF reduction is unknown, which raises concerns about breast cancer patients who are potentially cured. When trastuzumab is used as a single agent, cardio toxicity has been reported in up to 7% of patients. While, when combined with an anthracycline, TIC is notably increased up to 27% of cases, with NYGH Gr III or IV CHF being reported in 16% of patients in pivotal trials (4).

The NSABP B-31 (National Surgical Adjuvant Breast and Bowel Project) reported old age, baseline LVEF of 50%-54% and post-anthracycline LVEF of 50%-54% as significant risk factors of cardio toxicity (5). Cardiac arrhythmias and other cardiac risk factors were not found to be risk factors for cardiac toxicity in NSABP B-31 and (NCCTG N9831) of North Central Cancer Treatment Group (6,7). Nevertheless, other trials have not yet reported analysis of the predictive factors of trastuzumab induced cardiac dysfunction.

We aim to report the prevalence of cardio toxicity in her2 breast cancer Saudi population and to identify the subgroup of patients who are at higher risk to develop TIC by studying the various risk factors such as age, obesity, diabetes, hyperlipidemia and hypertension.

Patient and Methods

Using an institutional medical records database, we identified all early and advanced BC patients treated with trastuzumab at Adult Medical Oncology, KAMC-NGHA, Riyadh, from 1 March 2003 to 30 June 2012. 150 patients were identified and 104 were eligible for the study, they were Her2 positive breast cancer with good quality baseline 2D-echocardiogram, and LVEF ≥ 55%,

treated with trastuzumab and had received at least one dose of a trastuzumab-based regimen.

The following data were extracted retrospectively from electronic medical records for each patient: age, tumor characteristics, body mass index, chemotherapy use, smoking history, breast cancer side, use of radiation therapy, trastuzumab schedule and cardiac risk factors. These risk factors included hypertension (defined as blood pressure >140/90 mm Hg maintained over time or use of antihypertensive drugs), hypercholesterolemia (defined as total plasmatic cholesterol >200 mg/dl or use of lipid-lowering medications), diabetes mellitus (diagnosed by WHO criteria as fasting serum glucose ≥ 126 mg/dl, 2-h post challenge serum glucose ≥200 mg/dl or use of hypoglycemic medications).

All patients underwent a comprehensive baseline cardiac examination and echocardiography 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. This study was approved by the Medical Scientific Committee of the Institute and by the Local Ethics Review Board.

Statistical Analysis
Descriptive statistics were used to describe the number of patients experiencing a LVEF reduction. Student t-test was used to compare the different groups in regard to continuous variables eg. EF results before and after trastuzumab. The association between patients who experienced a cardiac event and the risk factors under investigation was analyzed with the x^2
test. Logistic regression was used to estimate OR and their 95% CI in order to evaluate the relation between cardiac risk factors and the development of cardio toxicity. All analyses were performed using SAS statistical (V.9.1, SAS Institute, Cary, North Carolina, USA). Statistical significance for all tests was taken as p<0.05.

Results

Patient Characteristics
A total of 104 Her2-positive BC patients met inclusion criteria. All patients had undergone surgical removal of breast cancer before adjuvant chemotherapy. Full baseline characteristics are listed in table 1. Median age at the start of trastuzumab therapy was 49 years (range 29-78 years), 15% were <40 years, and 40% were between 41 and 50 years of age.

The median BMI was 30.5 (range 25-34) with 60% of study population having values >30. The median LVEF value at baseline (before trastuzumab treatment) was 54.86 (range 50-55). The majority of patients (62.5%) were not treated with an anthracycline-based, whereas 37.5% were anthracycline-based chemotherapy (FEC, AC or FAC). There was no concurrent use of trastuzumab and anthracycline in any study patient.

66 patients (63.46%) did not have any cardiac risk factors at baseline, while the remaining 38 patients (36.54%) showed at least one risk factor: hypertension 23 (22.12%), diabetes mellitus 22 (21.15%) or hypercholesterolemia 17 (16.35%), hypothyroidism was seen in only 2% of study population, and none of them was a smoker.

Table 1: Baseline patients and disease characteristics (n=104)

Characteristics	N (%)	Median	Range
Age		49	29-78
<40	16 (15.38%)		
41-49	37 (35.58%)		
50-59	28 (26.92%)		
≥ 60	23 (22.12%)		
BMI		30.51	25.47 – 34.01
<20	7 (6.73%)		
20-24	11 (10.58%)		
25-29	23 (22.12%)		
≥ 30	63 (60.58%)		
Baseline LVEF%		54.86	50-55
Hypercholestrolemia			
Yes	17 (16.35%)		
No	87 (83.65%)		
DM			
Yes	22 (21.15%)		
No	82 (78.85%)		
Anthracycline			
Yes	39 (37.5%)		
No	65 (62.5%)		
HTN			
Yes	23 (22.12%)		
No	81 (77.88%)		
Hypothyroidism			
Yes	2 (1.92%)		
No	102 (98.08%)		

Cardiotoxicity and Potential Risk Factors
A cardiotoxic event was defined as an absolute LVEF reduction of at least 5 percentage points from baseline with signs and symptoms of heart failure (HF) or >10% without such symptoms. Recovery from the cardio toxic event was defined as LVEF recovery to values >50% or the complete resolution of symptoms. We used the term HF to denote New York Heart Association (NYHA) class III or IV cardiac dysfunction in the presence of decreased LVEF.

Of the 104 BC patients, only 16 (15.38%) experienced TIC event after a mean exposure duration of 15-month to trastuzumab (range 4-33 m), 8 patients stopped trastuzumab due to TIC after the first event and 3 patients after the second one. In our series trastuzumab induced significant decline in LVEF ended up with symptomatic CHF in 4 patients with subsequent irreversible none symptomatic EF < 55%.

Rate factors analysis
19 patients out of 104 (15.38%) developed trastuzumab induced cardiac toxicity (TIC). The distribution of possible risk factors in patients with and without trastuzumab-induced cardiotoxicity (TIC) is listed in table II. There was no statistically significant difference between the 2 groups for age, BMI, nor hypertension suggesting by this univariate analysis that those might not be an important risk factor for TIC, of the 16 patients with TIC, 4 patients (25%) were <40 years of age and only 1 patient (6%) was >60 years of age, compared to 12 patients (13.6%) and 22 patient (25%) of respectable age group from the 88 patients with no reported TIC, also the BMI of value >30 was seen in 10 patients (62%) in the TIC group vs 53 patient (60%) in patients without TIC, hypertension was reported in 6 patients (37%) from the TIC group vs 17 patients (19%) of patients without TIC, the difference was not statistically significant (P-value 0.1070).

On the other hand using the same univariate analysis, the presence of hypercholesterolemia, diabetes mellitus and the use of anthracycline were significant risk factor for the development of cardiac toxicity, as 11 patients of TIC group (64%) had hypercholesterolemia compared to 6 patients only from patients without TIC (7%), with highly statistical significant P-value of (0.001), as for the effect of diabetes, 7 patients from the TIC group (43%) had diabetes compared to 15 patients from patients without TIC (17%) with statistical significant P-value of (0.001), also 10 patients of TIC group (62%) had received anthracycline chemotherapy compared to 29 patients only from patients without TIC (33%) with statistical significant P-value of (0.025).

Table 2: Distribution of possible risk factors in patients with and without cardiotoxicity (n=104)

Factors	Pt with cardiotoxicity	Without cardiotoxicity	P-value
Age			
<40	4 (25.00%)	12 (13.64%)	
41-49	7 (43.75%)	30 (34.09%)	
50-59	4 (25.00%)	24 (27.27%)	
≥ 60	1 (6.25%)	22 (25.00%)	0.2994
BMI			
<20	00 (00%)	7 (7.95%)	
20-24	1 (6.25%)	10 (11.36%)	
25-29	5 (31.25%)	18 (20.45%)	
≥ 30	10 (62.50%)	53 (60.24%)	0.5063
Hypercholesterolemia			
Yes	11 (64.71%)	6 (6.81%)	
No	5 (5.75%)	82 (93.29%)	0.0001
DM			
Diabetic	7 (43.75%)	15 (17.05%)	
Non diabetic	9 (56.25%)	73 (82.95%)	0.0161
Anthracycline			
Yes anthracycline	10 (62.50%)	29 (32.95%)	
No anthracycline	6 (37.50%)	59 (67.05%)	0.0247
Hypertension			
Hypertensive	6 (37.50%)	17 (19.32%)	
Non	10 (62.50%)	71 (80.68%)	0.1070

On multivariate analysis (table III) statistically significant trastuzumab induced cardiac toxicity (TIC) was documented in association with hypercholesterolemia and the use of anthracycline on the other hand, it had failed to confirm the relationship of hypertension or diabetes to the development of TIC.

The OR for the presences of hypercholesterolemia was very high at 71.2 with very statistically significant P-value of .0001 while the OR for the use of anthracycline was 5.9 with P-value of 0.043. The differences observed for all other potential risk factors were not statistically significant.

Table 3: Multivariate analysis of risk factors in patients with and without cardiotoxicity (n=104)

Factors	OR	(95% CI)	P-value
Age			
<40 vs. ≥60	2.638	(0.122 – 56.842)	0.6785
41-49 vs. ≥60	8.013	(0.391 – 164.349)	0.2502
50-59 vs. ≥60	8.503	(0.407 – 177.624)	0.2318
BM			
20-24 vs. ≥30	1.073	(0.036 – 31.717)	0.6307
25-29 vs. ≥30	5.772	(0.746 – 44.648)	0.1450
Hypercholesterolemia			
High vs. normal	71.24	(9.217 – 555.657)	0.0001
DM			
Diabetic vs. non	3.217	(0.656 – 15.774)	0.1498
Anthracycline			
Anthracycline vs. anthracycline	5.928	(1.0153 – 33.358)	0.0435
Hypertension			
Hypertensive vs. non	2.372	(0.386 – 14.578)	0.3511

Discussion

Approximately 20-25% of breast cancer overexpresses the human epidermal growth factor II (Her2) which confers aggressive behavioral traits (12). In Saudi Arabia, breast cancer ranked the highest among Saudi females, comprising 27.7% of all malignancies (13) in the range between 17% as reported in the eastern region of the kingdom to 30% in the central region (14,15).

Although trastuzumab is not known to cause the classical toxicities related with chemotherapy or other targeted therapy medications, one of the major concern is the occurrence of cardiac dysfunction. The risk for serious and life-threatening cardiotoxicity with combination anthracyclines and trastuzumab has been an ongoing concern (16). Therefore, we designed this study with the aim of identifying the potential risk factors for cardiac toxicity associated with trastuzumab treatment among Saudi women with Her-2 positive breast cancer.

In our study, TIC defined as significant decline in the LVEF to below 55% was reported in 15% of the patients. Compare to around 4-5% in international series, an observation which may indicate different natural history among Arab women. Our series constituted of relatively younger patient population (median 45 years) where anthracycline is more frequently used compared with older patients as the median age in published pivotal randomized trials is >50 years (17, 18). Such a rational, which was the impetus of a recent study assessing cardiac events in elderly breast cancer women between 72-90 years (19).

It is worth noting that our study have limitations in interpreting results given its retrospective nature and the small sample size, which limited its power to detect statistical have limitations in interpreting results given its retrospective nature and the small sample size, which limited its power to detect statistical significant parameters. However, such limitations are encountered and shared in recently published reviews in the west (20), as well as a single Saudi institution series (21) which retrospectively published data of 98 patients who received adjuvant trastuzumab from 2006 to 2009. More or less the results matched our report in terms of TIC detected among 12% of cases (11/98). Furthermore, 5 patients suffered CHF subsequent withdrawal of trastuzumab.

Moreover, our study demonstrated a significantly increased incidence of cardiac events with multivariate analysis among patients with history of DM and hyperlipidemia similar to published reports, but the only statistically significant risk factors identified on multivariate analysis was hypercholesterolemia and previous anthracycline exposure while other well- known established risk factors such as hypertension, left side breast and were not shown to have a significant impact on development of trastuzumab-induced cardiac toxicity among our population, (22), the reason might be the relatively small sample size of our study.

A median BMI of 31.22 was reported among the 16 patients who suffered trastuzumab induced cardiotoxicity compared to BMI of 30.51 of the whole study group with no statistical significant difference (P-value 0.56). Other studies had suggested that a BMI of more than 25 have been shown to increase the risk of cardiac toxicity but the results are inconsistent or uniform (3, 9). The main preventive strategy would be through early detection of high risk patients and prompt initiation of prophylactic treatment, so it seems of crucial importance to identify patients with DM and hyperlipidemia before treatment with trastuzumab, such patients require cautious follow-up and close monitoring and early intervention to avoid any deterioration of the cardiac function.

Detection of subclinical myocardial changes might be proven very important for better patient selection, the role of troponin I (TNI) in relation TIC was recently reported, 72% of patients who had elevated levels of TNI had TIC compared to 7% of those with normal levels (23, 24).

Several other methods are currently been explored for early detection of subclinical LV dysfunction as the new echocardiographic methods such as myocardial strain and strain rate (SR) are newer echocardiographic parameters using promising tools as tissue Doppler imaging (TDI) or speckle tracking (ST), cardio specific biomarkers NT-proBNP (25) or innovative Her-2 imaging techniques which may prove of use in the near future (26).

Whether we encourage the concept of substituting anthracyclines by evidence-based alternatives as TCH from BCIRG006 (27) which reported cardiac event rate of 0.4% is still controversial since we lack long term cardiac safety profile of the treated patients.

Conclusion and Recommendations

Although TIC is not a common adverse event, it is very important to know the patients who are at risk, as prevention and early treatment might be very effective to optimize outcome of trastuzumab therapy. In our study, we have found that hyperlipidemia and the use of anthracycline are considered significant independent risk factors for exacerbating trastuzumab induced cardiac toxicity. While, in our study, hypertension, diabetes nor high BMI values did not correlate with the development of trastuzumab induced cardiac toxicity, an observation which needed to be interpreted with a lot of caution due to small sample size, and the fact the majority of such patients are already taking AC inhibitors.

Risk factors for trastuzumab-related cardiotoxicity are still poorly defined and are generally considered to be similar to those for anthracycline-induced cardiac dysfunction. Further research is needed to determine predictive factors for the early occurrence of cardiotoxicity in order to prevent cardiac injury.

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