Internal Medicine: Open Access

Farhoud and khalifa, Intern Med 2018, 8:3
DOI: 10.4172/2165-8048.1000275

Research Article Open Access

Trastuzumab Related Cardio-toxicity in Breast Cancer Patients Single Center Experiences

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Received date: May 15, 2018; **Accepted date:** May 21, 2018; **Published date:** May 24, 2018

Abstract

Background: Trastuzumab may induce cardio-toxicity which can be clinically identified as decreased left ventricular systolic function with or without symptoms of heart failure.

Objectives: To determine the prevalence and potential risk factors of trastuzumab related cardio-toxicity in breast cancer treated patients.

Methods: The study was carried out on 78 HER2- positive breast cancer patients who received trastuzumab in the Oncology Department of Al-yarmouk teaching hospital, Baghdad, between September, 2017 and April, 2018.

Results: Seventy-eight patients, median age 57 years (range 41-72), were identified. Twenty one (26.9%) patients developed a significant declining in left ventricular systolic function (26.6% of early breast cancer patients and 27.2% of patients with metastatic disease).

Six of 78 patients (7.6%) developed symptomatic heart failure. Patients with trastuzumab-related cardiotoxicity presented more often with lower baseline ejection fraction, negative estrogen and progestron receptors, prior radiotherapy, diabetes mellitus and higher body mass index.

Conclusion: Trastuzumab not uncommonly induce cardiac toxicity that mainly manifested as left ventricular systolic dysfunction. The routine assessment of left ventricular systolic function before and during the course of trastuzumab therapy should be considered.

Keywords: Breast cancer; Cardio-toxicity; Risk factors; Trastuzumab

Introduction

Trastuzumab is a monoclonal antibody, directed against the human epidermal growth factor receptor 2 (HER-2). HER2 act as a transmembrane receptor tyrosine kinase which is important for cell growth and proliferation in addition to its importance for "myocardial protection against ischemia or adrenergic stimulation". About 20% of breast cancer patients have overexpression of HER2 and its associated with poor prognosis [1].

Cardiac toxicity is one of the common complications that related to trastuzumab therapy which can be identified as symptomatic or asymptomatic left ventricular systolic dysfunction.

As adjuvant therapy, its recommended that trastuzumab (Herceptin) is given intravenous infusion weekly for 12-18 week then every 3 weeks for one year (52 week), either as a mono therapy or in combination with chemotherapeutic or hormonal agents , whereas in the treatment for metastatic disease, trastuzumab is continued until disease progression or harmful toxicity happened [1].

The incidence of heart failure during trastuzumab therapy is estimated at about 4-7% and this cardio-toxic effect may reach 27% in anthracyclines containing regimens [2]. The mechanism of trastuzumab-related cardiac toxicity is different from that of anthracycline cardio-toxicity by the absence of ultra-structural damage or cellular death in cardiac myocyte. Additionally, trastuzumab related cardiac toxicity seems to be not dose depended which is differ from cardiac side effects that caused by anthracycline therapy.

Importantly, trastuzumab related cardiac toxicity seems to be reversible or partially reversible and patients usually improve after discontinuation of the treatment for 4-8 weeks. However, to achieve this improvement, many patients need specific anti-failure treatment [3-5].

The mechanism of cardiac toxicity that occurs in trastuzumab therapy is not completely understood. Some previous reports stated that it may be related to the HER2 receptor that present on the surface of cardio-myocytes.

Transthoracic echocardiography is an acceptable, widely available, and noninvasive imaging study for assessment and monitoring trastuzumab related cardio-toxicity which includes measurement of cardiac dimensions, systolic and diastolic left ventricular function, right ventricular dimensions and contractility, pericardial abnormalities and others parameters.

Current guidelines recommend that patients treated with trastuzumab undergo cardiac monitoring before starting treatment

(baseline reading) and then every 3 months during treatment courses [6-8].

Patients with an asymptomatic decline in LVEF by 15% (or by 10%, if the baseline LVEF equal or lower than 50%) require discontinuation of trastuzumab therapy [6].

The aim of our study was to identify the precise prevalence of cardio-toxic effect of trastuzumab and its potential risk factors in breast cancer treated patient that seems to be underestimated.

Materials and Methods

This study was conducted in Oncology Department of Al yarmouk teaching hospital/ Baghdad between September, 2017 and April, 2018.

We included breast cancer patients with HER2 receptor overexpression that was checked by immunohisto-chemical method (IHM) in postoperative specimens or biopsy samples.

Transthoracic echocardiography was performed for the patients at least one time before and during trastuzumab treatment courses for early or metastatic disease.

Heart failure symptoms were classified according to the New York Heart Association (NYHA) functional system.

Assessment of left ventricular systolic function with transthoracic echocardiography including LV internal dimensions (LV end systolic and diastolic dimensions), LV ejection fraction (LVEF% using Teichholz methods) and LV contractility, all transthoracic echocardiographic examinations were obtained using GE Vivid E9 machine with 4 MHz probe and performed according to the recommendations of American Society of Echocardiography.

Cardio-toxicity was defined as an absolute drop >15% of the baseline normal LVEF.

The following patients were excluded from the study:

- Patients with baseline LVEF <50%
- Patients with unstable ischemic heart disease.
- Patients with significant valvular heart disease.
- Patients with uncontrolled hypertension.
- Patients with uncontrolled diabetes.
- Patients that received prior or concomitant well known cardio-toxic chemotherapeutic agent (e.g. anthracyclines).

Statistical analysis

"Analysis of data was carried out using the statistical package of SPSS-22 (Statistical Packages for Social Sciences-version 22). Data were presented in simple measures of frequency, percentage, mean, standard deviation, and range (minimum-maximum values)".

"The significance of difference of different means (quantitative data) was tested using Students-t-test for difference between two independent means. The significance of difference of different percentages (qualitative data) was tested using Pearson Chi-square test (^{2}-test). Statistical significance was considered whenever the P value was equal or less than 0.05"

Results and Discussions

Seventy-eight breast cancer patients were included in this study.

The median age was 57.2 ± 8.8 years (range: 42-73 years).

Forty-five patients (57.7%) were categorized as patients with early breast cancer and 33 (42.3%) patients with metastatic disease (Table 1).

Variables	All patients (n=78), n%	Patients with cardiac toxicity (n=21), n%	Patients without cardiac toxicity (n=57), n%	P value
Age (year)				
<50	14 (18)	3 (14.3)	11 (19.3)	-
50-60	29 (37.1)	11 (52.4)	18 (31.6)	0.721
>60	35 (44.9)	7 (33.3)	28 (49.1)	-
Menopausal state				
Pre-menopause	22 (28.2)	8 (38)	14 (24.6)	0.423
Post-menopause	56 (71.8)	13 (62)	43 (75.4)	-
Stage				
1	22 (28.2)	4 (19)	18 (31.6)	0.823
2	37 (47.4)	11 (52.4)	26 (45.6)	-
3	19 (24.4)	6 (28.6)	13 (22.8)	-
Grade				
Well differentiated	12 (15.4)	3 (14.3)	9 (15.7)	0.642
Moderately differentiated	34 (43.6)	7 (33.3)	27 (47.4)	-

Poorly differentiated	22 (28.2)	8 (38)	14 (24.6)	-
Undifferentiated	4 (5.1)	1 (4.8)	3 (5.3)	-
Unknown	6 (7.7)	2 (9.5)	4 (7)	-
Tumor size				
<2 cm	25 (32)	6 (28.6)	19 (33.3)	0.842
2-5 cm	42 (53.8)	11(52.4)	31 (54.4)	-
>5 cm	11 (14.1)	4 (19)	7 (12.3)	-
Nodal status				
No	21 (27)	6 (27.3)	15 (26.8)	0.821
3-Jan	36 (46.1)	8 (41)	28 (50)	-
>3	14 (18)	5 (22.7)	9 (14.3)	-
Unknown	7 (8.9)	2 (9)	5 (8.9)	-
Estrogen receptors				
Positive	42 (53.8)	6 (28.6)	36 (63.2)	0.05*
Negative	25 (32.1)	12 (57.1)	13 (22.8)	-
Unknown	11 (14.1)	3 (14.3)	8 (14)	-
Progesterone receptor				
Positive	23 (29.4)	4 (19)	19 (33.3)	0.032*
Negative	41 (52.6)	15 (71.4)	26 (45.6)	-
Unknown	14 (18)	2 (9.5)	12 (21)	-
Hormonal receptors status (ER or PR)				
Positive	49 (62.8)	6 (28.6)	43 (75.4)	-
Negative	24 (30.8)	13 (61.9)	11 (19.3)	0.05*
Unknown	5 (6.4)	2 (9.5)	3 (5.3)	-
Radiotherapy				
Yes	33 (42.3)	15 (71.4)	18 (31.6)	0.03*
No	45 (57.7)	6 (28.6)	39 (68.4)	-

Table 1: Patients demographic and baseline characteristics.

Forty two patients (53.8%) had positive estrogen receptor and 23 patients (29.4%) had positive progesterone receptor. Estrogen or progesterone receptors were negative in 24 patients (30.8%). There was a significantly higher occurrence of cardiac side effects in patients with negative receptors status compared with positive receptors status (61.9% versus 28.6% respectively, $p<0.05$).

Thirty three (42.3%) patients exposed to prior or concomitant radiotherapy to the left side of the chest.

No statistically significant relationship was noted between the number of trastuzumab doses or duration of treatment and cardiac toxicity.

The declining in LVEF was significantly higher in patients with BMI equal or more than 30 ($p<0.05$) (Table 2).

Co-morbidity	All patients (n=78), n%	Patients reducing LVEF (n=21), n%	Patients without reducing LVEF (n=57), n%	P value

Hypertension	37 (47.4)	12 (57.1)	25 (43.8)	0.723
DM	14(18)	9 (42.8)	5 (8.7)	0.032*
BMI>30	29 (37)	14 (66.7)	15 (26.3)	0.043*
Dyslipidemia	23 (29.5)	8 (38)	15 (26.3)	0.342
Renal impairment	9 (11.5)	4 (19)	5 (8.7)	0.421
No. of risk factors				
Non	42 (55.1)	8 (38)	34 (59.6)	0.324
2-Jan	27 (34.7)	10 (47.6)	17 (29.8)	-
3 or more	9 (10.2)	3 (14.3)	6 (10.5)	-
Baseline LVEF (%)				
<60	27 (34.6)	12 (57)	15 (26.3)	0.05*
>60	51 (65.4)	9 (43)	42 (73.7)	-

Table 2: LVEF changes during trastuzumab therapy.

We noted a significantly higher prevalence of trastuzumab related LV systolic dysfunction in diabetic patients ($p<0.05$) whereas there was no significant relationship observed between trastuzumab related cardiac toxicity and the presence of other risk factors like age, postmenopausal status, hypertension, hyperlipidemia and renal impairment.

Baseline LVEF ranging between 53% and 72%.

In 27 patients (34.6%), LVEF values were between 53% and 59% and in 51 patients (65.4%) LVEF values were between 60% and 72% (Table 2).

The declining of LVEF was significantly higher in patients group with baseline LVEF was lower than 60% comparing with patients group with higher baseline LVEF ($p<0.05$).

A total of 21 patients (26.9%) had a significant decline in LVEF during treatment courses comparing with baseline values (Table 3).

Parameter	**Adjuvant therapy (n=45), n%**	**Metastatic disease (n=33), n%**	**P value**
Significant decline in LVEF	12 (26.6)	9 (27.2)	0.642
Asymptomatic HF	11 (24.4)	4 (12.1)	0.112
Symptomatic HF	2 (4.4)	4 (12.1)	0.082
Arrhythmias (AF)	-	2 (6)	-
RV dysfunction	2(4.4)	1 (3)	0.834
Pericardial effusion	4 (8.8)	2 (6)	0.754
*p value<0.05 is considered statistically significant			
LVEF: Left Ventricular Ejection Fraction; HF: Heat Failure; AF: Atrial Fibrillation; RV: Right Ventricle			

Table 3: A comparison of trastuzumab related cardiac side effects in adjuvant therapy and treatment of metastatic disease.

No significant difference was noted in the occurrence of cardio-toxicity between patients treated with trastuzumab as an adjuvant therapy and patients treated for metastatic disease, (26.6% versus 27.2%, respectively; p=0.642).

According to NYHA classification, six patients (7.6%) developed symptoms of heart failure (four patients with metastatic disease); three of them experienced symptoms of class III.

Six patients had a mild pericardial effusion, three patients developed RV dilatation with systolic dysfunction, and two patients developed rapid atrial fibrillation.

The using of trastuzumab increasing significantly during the last two decades for the treatment of breast cancer patients as an adjuvant therapy and for metastatic disease, one of the common side effects of trastuzumab (Herceptin) is cardiac toxicity that manifested as symptomatic or asymptomatic systolic heart failure or cardiomyopathy in addition to other cardiac complications like arrhythmias, right ventricular dysfunction and pericardial effusion.

Trastuzumab treated patients may presented with typical symptoms of systolic heart failure like exertional dyspnea, fatigue and signs of volume overloud (e.g. elevated jugular venous pressure and bilateral leg edema). But the commonest cardio-toxic effect noted with trastuzumab therapy is asymptomatic (subclinical) decline in LVEF.

Most of previous reports showed increased risk of trastuzumab cardiac toxicity when used in combination with anthracycline and currently, many oncologists are trying to avoid using this combination [9,10] and that is why we excluded patients received this combination of therapy from our study.

In the HERA trial [10] asymptomatic decline in LVEF was noted in 7.1% of patients whereas 1.7% of patients presented with symptomatic heart failure.

In the NSABP B31 trial [11] trastuzumab therapy was discontinued in 14.2% due to asymptomatic decline in LVEF and in 4.7% of patients due to symptomatic left ventricular dysfunction.

Serrano et al. [12], reported that "Cardiac side effects caused by trastuzumab developed in 26.7% of patients, including symptoms of heart failure in 8.9%".

In this study, a significant decline in LVEF was noted in 26.9% of the included patients. From the total of 78 included patients, symptoms of heart failure were noted in six (7.6%) patients.

We noted a statistically significant difference in the declining of LVEF between patients with baseline LVEF less than 60% and in those patients with LVEF were equal or more than 60% ($p<0.05$) and this was comparable to previous mentioned studies.

Presence of diabetes mellitus was a major independent risk factor for the occurrence of cardio-toxicity in trastuzumab treated breast cancer patients and we observed that a statistically significant relationship between the presence of diabetes mellitus and the development of cardiac toxicity ($p=0.032$) which was also comparable to previous reports.

Interestingly, the declining of LVEF was significantly higher in patients with BMI equal or more than 30 ($p<0.05$) and this unexplained finding was comparable to Serrano et al. [12] and Suter et al. [13] results and also similar to the finding of HERA trial [10].

In the NSABP B31 trial [11], age>60 years was noted to be a risk factor for cardio-toxicity. Similar finding was observed in the North Central Cancer Treatment Group (NCTG) N9831 trial [14].

Older age had a non-significant impact on the development of cardiac complications which is may be explained by a small sample size due to strict exclusion criteria that we applied in this report.

Trastuzumab related cardiac toxicity was significantly higher in those patients exposed to prior radiotherapy which is also comparable to above mentioned reports.

Other risk factors that may increase the risk of trastuzumab related cardiac toxicity like presence of hypertension, dyslipidemia and menopausal state showed no significant impact on the development of asymptomatic or symptomatic left ventricular systolic dysfunction. Serrano et al. [12] reported in their study that "well-known cardiac event-related factors, such as hypertension and a smoking, were not demonstrated to increase trastuzumab-related cardio-toxicity".

The NSABP B-31trail [11] identified four risk factors for trastuzumab related cardio-toxicity: older age, hypertension, lower baseline LVEF (50%-54%), and concomitant anthracycline therapy.

We noted in our study that there was no direct relationship between the number of trastuzumab doses or duration of treatment and the development of cardio-toxicity and many patients received trastuzumab for long period without evidence of cardiac complications which may leads to the conclusion that trastuzumab related cardiac toxicity may be unpredictable.

In this study, patients with negative estrogen or progesterone receptors expression were more likely to developed trastuzumab related cardio-toxicity compared with patients with positive receptors status (59% versus 21.4% respectively, $p<0.05$). This was similar to previous mentioned studies and this finding is explained by the role of estrogen and progesterone for protection of myocardium against ischemic changes [15].

We observed in this study that prior or concomitant exposure to radiotherapy of left side of the chest was strongly associated with occurrence of trastuzumab cardiac toxicity ($p=0.03$) and this is also comparable to the prior mentioned studies. Joanna et al. [16] who reported in their study that patients with older age who received radiotherapy were more likely to develop cardio-toxicity ($p=0.0003$).

Finally, we not observed a statistically significant difference in the development of cardiac side effects like left ventricular dysfunction, arrhythmias, right ventricular dysfunction and pericardial effusion between patients received adjuvant therapy and patients treated for metastatic disease.

Limitations

First, a strict exclusion criterion in our study may explain small sample size and this may give selection bias.

Second, this is an observational study and a larger study is needed for long term follow up to determine the reversibility and impact of medical treatment and prognosis for trastuzumab related cardio-toxicity.

Third, we depend mainly on echocardiography for detection of myocardial dysfunction and actually using of biomarkers or novel imaging techniques like cardiac MRI can help in this issue.

Conclusion

Prior radiotherapy to the left side of the chest, presence of diabetes mellitus, higher BMI, low baseline LVEF and negative steroid receptor status are a potential risk factors for trastuzumab related cardiac, accordingly patients with one or more of these risk factors should be monitored more frequently.

There was no significant difference in occurrence of trastuzumab related cardio-toxicity between patients receiving adjuvant therapy and patients treated for metastatic disease.

Ongoing discussion and cooperation between oncologist and cardiologist is needed to optimize the medical care and decrease the risk of trastuzumab related cardio-toxicity.

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