

Incidence of trastuzumab-induced cardiotoxicity and impact of body mass index in patients with breast cancer: Results from a Saudi tertiary cancer center

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Abstract. The effect of BMI as a risk factor in trastuzumab-induced cardiotoxicity in Saudi patients with HER2-neu positive breast cancer treated with trastuzumab and anthracyclines is not fully understood. The present study retrospectively evaluated the overall incidence of cardiotoxicity and the effect of BMI as a risk factor for cardiotoxicity. A retrospective study performed between 2011 and 2015 of patients with Her2-neu positive early breast cancer who were treated with either a combination of trastuzumab and anthracycline or a combination of trastuzumab with non-anthracycline or hormonal treatment in the adjuvant settings was carried out. The incidence of cardiotoxicity and the effect of BMI, hypertension and diabetes mellitus as risk factors for cardiotoxicity were assessed. Cardiotoxicity was measured using a drop in the ejection fraction of >10 percentage points to a left ventricular ejection fraction of <50%. The present cohort included 105 patients diagnosed with stage I and II breast cancer. The mean age of the present cohort was 47.5±1.0 years (range, 25-76 years), the mean height was 153.9±14.1 cm (range, 126-170 cm), the mean body weight was 75.7±15.6 kg (range, 40-143 kg) and the mean BMI was 31.3±5.8 (range, 18-49). Cardiotoxicity was detected in 21.9% of the cohort. The BMI was calculated for 81 patients who were treated with a

combination of trastuzumab and anthracycline. Cardiotoxicity was detected in 3 out of 9 patients with a BMI <25, in 9 out of 23 patients with a BMI between 25 and 29, and in 6 patients with a BMI >30. There was a significant association between cardiotoxicity and BMI (P=0.03). No significant association between age, hypertension and diabetes and cardiotoxicity was identified. In conclusion, compared with global cohorts, the present results revealed a higher incidence of cardiotoxicity among Saudi patients with HER2-neu positive early breast cancer treated with trastuzumab combinations in adjuvant settings. Increased BMI was significantly associated with cardiotoxicity.

Introduction

Higher body mass index (BMI) is associated with an advanced stage of breast cancer and tumor size at the time of diagnosis (1). Obesity also negatively affects the outcome of breast cancer treatment modalities such as surgery, radiotherapy, chemotherapy, and hormonal therapy (2,3). Moreover, the negative effect of obesity on overall survival and disease-free survival was reported in breast cancer patients receiving doxorubicin-based chemotherapy (4). Conversely, some studies reported that BMI does not influence disease-free survival and overall survival.

Anthracyclines are anticancer agents with significant efficacy in treating patients with breast cancer. The use of anthracyclines, however, is limited by the cardiotoxicity they may induce (5). Furthermore, the sequential administration of trastuzumab (Herceptin[®]), a humanized monoclonal antibody against the human epidermal growth factor receptor 2 (HER-2) protein, in the settings of adjuvant therapy is effective in slashing the recurrence risk of breast cancer by one-half and the risk of death by one-third (6). Clinical studies reported that management with trastuzumab led to a significant

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reduction in the systolic ventricular function that may lead to heart failure (7,8). Adiponectin, an insulin-sensitizing and anti-inflammatory adipokine, acts as a crosslinker between obesity and obesity-induced disorders such as cardiovascular disease (9). It has been proposed that anthracycline-induced cardiotoxicity is promoted by obesity via Adiponectin down-regulation. In conjunction with that, Adiponectin knockout showed exacerbated left ventricular contractile dysfunction in response to doxorubicin in a mice model (10). However, Adiponectin has not been associated yet with trastuzumab-induced cardiotoxicity (TIC) (11). Only age and concomitant doxorubicin chemotherapy have been identified as significant risk factors for TIC (12).

Increasing evidence supports dosing monoclonal antibodies as a fixed-dose (13). Furthermore, monoclonal antibodies typically have a wider therapeutic window and would, therefore, be potentially amenable to fixed dosing (14).

Since the identification of risk factors for cancer patients and association with the treatment response can significantly improve the patient's outcome, the current study was designed to evaluate the incidence of cardiotoxicity in patients with HER2 neu positive breast cancer who have received either a combination of trastuzumab and anthracycline or other trastuzumab combinations and to study the impact of higher BMI, diabetes mellitus, and hypertension as risk factors for TIC. The difference between dosing with actual body weight (ABW) and ideal body weight (IBW) has been evaluated.

Materials and methods

Patient selection. This retrospective study including 105 adult breast cancer patients who were treated with either a combination of trastuzumab and anthracyclines or trastuzumab plus non-anthracycline or hormonal treatment in adjuvant settings. It was carried out between 2011-2015, where data was extracted from hospital files. The study aimed to assess the incidence of trastuzumab-induced cardiotoxicity and the impact of body mass index. Exclusion criteria included patients known to have cardiac disease and patients with metastatic disease. The ejection fraction (EF) was assessed for all patients by MUGA scan or ECHO every three months, or if the patients started to have symptoms of congestive heart failure, i.e., unexplained weight gain or dyspnea (15). The drop in EF was measured as the difference between baseline and worst EF percentage recorded during the following 12 months. Cardiotoxicity was defined as a drop of >10% to a left ventricular ejection fraction (LVEF) of <50% (16). Body mass index (BMI) was calculated per the world health organization definition as weight in kilograms divided by the square of height in meters (kg/m^2) (17). BMI >25 is overweight and >30 is obese. In obese patients, the IBW and ABW are used to calculate medication dosages in which the formula only applies to persons 152 cm or taller. IBW was calculated as $\text{ABW} = \text{IBW} + 0.4$. We computed IBW from body weight and height with 2.3 kg increase over 45.5 kg for each inch over 152 cm and 0.9 kg decrease over 50 kg for each inch below 152 cm.

Statistical analysis. Descriptive statistics were computed as a baseline frequencies and percentages depending on the type of available data. Precision-of-point estimates were estimated

using 95% confidence intervals (CI). Chi-square test was used for correlation between categorical variables. Univariate and multi-variate logistic regression analysis was carried out to find the variables of significant predictability. We used the software STATA v.13.0 (Stata Corp.) in our analysis. A statistical significance threshold of $P < 0.05$ was adopted.

Results

Baseline comorbidities and character. Our cohort included 105 patients. Some of the data for patients was missing owing to nonentry or missing files' sections. The mean age of our cohort was 47.5 ± 12 years (range 'r':25-76), mean height was 153.9 ± 14.13 (r :126-170 cm), mean body weight was 75.7 ± 15.6 (r :40-143 kg), and mean BMI was 31.3 ± 5.8 (r :18-49) (Table I). Hormone response was positive in 63 (60.6%), most common stage was III in 50 (47.6%), followed by II 48 (45.7%). A total of 20 (20%) of patients were Diabetic and 22 (22%) were hypertensive. Site of Cancer was mostly left-sided in 60 (61.9%). Anthracycline was administered to 81 (77.1%) of the patients. Seventeen cycles of Herceptin were completed in 66 (63%) of our patients. Radiotherapy was received by 85 (81.7%) of the patients (Table I).

Cardiotoxicity comparison with univariate analysis. We found cardiotoxicity in 23 patients 21.9% (mean 43.1 ± 3 , range: 35-49) of the cohort. 15 patients (18.5%) among which have received anthracycline (P -value 0.12), and significantly higher Cardiotoxicity in patients with less than 17 Herceptin cycles (P -value 0.03) (Table II). Of our cohort, 81 patients were treated with a combination of trastuzumab and anthracycline while 24 patients were treated with a combination of trastuzumab and hormonal treatment or taxane based therapy.

BMI was calculated for 81 patients treated with a combination of trastuzumab and anthracycline. The cohort comprised of 10 (12.3%) patients who had a BMI of <25, 23 (27.1%) had a BMI between 25-29, and 49 (60.4%) had a BMI of >30. There was a significant correlation between the cardiotoxicity and BMI groups (P -value 0.011) (Table III). Cardiotoxicity and BMI relationship was detected in 3 out of 10 patients with BMI <25, in 9 of 23 patients with BMI between 25-29, and in 4 patients with BMI >30. No significant association was found between age, hypertension, diabetes, and cardiotoxicity.

ABW and IBW basic statistical analysis. The mean difference in Trastuzumab dosage, when computed from ABW vs. IBW, was 165.5 mg, which translates into 2,805 mg extra dose administered for a total of 17 cycles per patient (Table IV).

Multivariate regression analysis. A univariate regression analysis is done to identify predictors of cardiotoxicity for positive and negative hormone receptors. For negative value of hormone receptor Anthracycline usage, and Radio therapy are the only variables showing significant predictability (P -value 0.019, 0.01) (Table V). For positive hormone receptor only stage and Herceptin cycle > 17 were of significance (P -value 0.03, 0.031).

A multivariate regression analysis is followed by the univariate analysis to identify predictors of cardiotoxicity for positive and negative hormone receptors. For negative

Table I. Baseline comorbidities and characteristics of the study cohort.

Variable	Value
Age	
No.	105
Mean, years	47.5
SD, years	12.0
Minimum, years	25
Maximum, years	76
Height	
No.	105
Mean, cm	153.9
SD, cm	14.1
Minimum, cm	126
Maximum, cm	170
Body weight	
No.	105
Mean, kg	75.8
SD, kg	15.6
Minimum, kg	40
Maximum, kg	143
BMI	
No.	104
Mean, kg/m ²	31.3
SD, kg/m ²	5.8
Minimum, kg/m ²	18
Maximum, kg/m ²	49
Hormone response, n (%)	
Negative	41 (39.4)
Positive	63 (60.6)
Stage, n (%)	
I	6 (5.8)
II	48 (45.7)
III	50 (47.6)
Diabetes, n (%)	
No	80 (80.0)
Yes	20 (20.0)
Hypertension, n (%)	
No	78 (78.0)
Yes	22 (22.0)
Site of cancer, n (%)	
Bilateral	1 (1.0)
Left	60 (61.9)
Right	36 (37.1)
Anthracycline, n (%)	
No	24 (22.8)
Yes	81 (77.1)
Herceptin cycle >17, n (%)	
No	39 (37.1)
Yes	66 (62.8)
Radiotherapy, n (%)	
No	19 (18.3)
Yes	85 (81.7)

Table II. χ^2 test for worse ejection fraction difference from baseline >10% compared with anthracycline usage.

Variable	Cardiotoxicity		P-value
	No	Yes	
Anthracycline			
No	16 (15.2)	8 (7.6)	0.12
Yes	63 (62.8)	15 (14.3)	
Herceptin cycle			
≤17	26 (24.8)	13 (12.4)	0.03
>17	56 (53.3)	10 (9.5)	

value of hormone receptor Anthracycline usage, and stage of cancer showed significant predictability (P-value 0.018, 0.042) (Table VI). For positive hormone receptor no significance was found. Radiotherapy was excluded as multivariate regression failed to converge in its presence.

Anthracycline was significant for negative hormone receptor while being insignificant for positive hormone receptor. Site of cancer was insignificant for both negative and positive hormone receptor. Stage of cancer was significant for negative hormone receptor only. Hypertension and Diabetes were also insignificant. In conclusion, Anthracycline was the only variable showing significance for univariate and multivariate analysis for negative hormone receptor.

Discussion

Trastuzumab and anthracyclines are two main chemotherapeutic agents in breast cancer management. Although anthracyclines have proven efficacy and extensive use in adjuvant and palliative treatment regimens, they can induce a myriad of toxic effects such as mucositis, hair loss, myelosuppression, and cardiotoxicity (13). The latter is the most prominent risk, causing multimorbidity and thereby negatively impacting quality of life. Cancer-related cardiac dysfunctions are one of the most feared side effects of chemotherapy, occurring in about 10% of patients (18). While HER2 overexpression is reported in 20-25% of breast cancer cases (19). Trastuzumab is a mandatory drug used in HER2 expressing breast cancers, with one of the major side effects being cardiotoxicity and therefore requiring close monitoring (20).

Chemotherapy-induced cardiotoxicity is defined by the National Cancer Institute as 'toxicity affecting the heart' (21). However, the Cardiac Review and Evaluation Committee supervising trastuzumab clinical trials defined cardiotoxicity as one or more of the following conditions: a reduction of LVEF either globally or affecting the septum, symptoms and/or signs of heart failure regardless of LVEF value, or a reduction of greater than 10% from baseline LVEF with no signs or symptoms of heart failure (22). In the current study, a similar definition was followed for the indication of cardiotoxicity, i.e., a reduction of >10% from baseline LVEF to an LVEF of <50% (16). The PERSEPHONE phase-III trial, with its non-inferior design on 4,089 randomized patients, showed the edge a 6-month trastuzumab regimen has over a 12-month

Table III. χ^2 test for cardiotoxicity vs. BMI in patients who received a combination of anthracycline and trastuzumab.

Cardiotoxicity	BMI <25, n (%)	BMI 25-29, n (%)	BMI \geq 30, n (%)	Total, n (%)	P-value
No	7 (8.6)	14 (17.3)	45 (55.5)	66 (81.5)	0.011
Yes	3 (3.7)	9 (9.8)	4 (4.9)	15 (18.5)	

Table IV. Mean, SD and range of trastuzumab dose based on IBW and ABW calculations, with the difference of dose calculation between ABW and IBW in the last row.

Variable	No.	Mean	SD	Range	
				Minimum	Maximum
IBW dose, mg	105	294.0	29.4	217.7	370.8
ABW dose, mg	105	459.6	92.1	280.0	790.0
Difference between ABW and IBW, mg	105	165.5	89.9	-51.8	495.3

ABW, actual body weight; IBW, ideal body weight.

Table V. Univariate logistic regression analysis of cardiotoxicity and patient variables.

Variable	Hormone receptor-negative			Hormone receptor-positive		
	Regression coefficient	P-value	95% CI	Regression coefficient	P-value	95% CI
Cardiotoxicity						
Anthracyclin	-2.00	0.019	-3.6, -0.3	0.02	0.970	-1.4, 1.4
Site of cancer	-0.65	0.380	-2.0, 0.8	0.24	0.720	-1.0, 1.5
Stage	-1.11	0.070	-2.3, 0.1	1.50	0.030	0.2, 2.8
Herceptin cycle >17	-0.66	0.350	-2.0, 0.7	-1.50	0.031	-2.9, -0.1
Hypertension	-1.40	0.200	-3.6, 0.8	-0.36	0.660	-2.0, 1.3
Radiotherapy	-2.00	0.010	-3.6, -0.5	-	-	No observation
Diabetes	-1.25	0.271	-3.4, 0.9	0.47	0.550	-1.1, 1.9

95% CI, 95% confidence interval.

one in lowering the incidence of TIC (23). In contrast to our findings, a meta-analysis capturing 6,527 patients reported an association between TIC and hypertension ($P < 0.01$), diabetes ($P < 0.02$), anthracycline ($P < 0.02$), and older age ($P = 0.013$) (24). In another meta-analysis of an adjuvant setting in which trastuzumab use in conjugation with chemotherapy was found to lower mortality and improve relapse risk by one-third, a TIC risk of two to three times was reported as well (25). In a pivotal multicenter phase-III trial, Slamon and Pegram (26) reported heart failures in 27% of HER2-positive metastatic breast cancer patients treated with a trastuzumab and anthracyclines combination, while cardiac dysfunctions occurred in less than 7% in the anthracyclines-only group.

In our cohort, cardiotoxicity was reported in 21.9% of patients compared to around 4-5% in international series,

an observation that may indicate different natural history among Arab women. Young patients account for the majority of our cohort (median 47 years) in which anthracycline is frequently used compared to older patients with median age >50 years in western series (27,28). Interestingly, our cohort showed conflicting results of TIC compared with other regional single-institution studies. Ours was significantly higher than those reported by Abulkhair *et al* (29) at 12% and Aldiab (30) at 11%, but lower than that found by Alghafar *et al* (31) at 24% and Hamed *et al* (32) at 35%. Furthermore, 75% of the patients in Hamed *et al's* study (32) were young. In complete accordance with our study are the results of Abdel-Razaq *et al* (33), who reported 21.9% TIC in 146 patients from two local hospitals in a study spanning almost 3 years.

Table VI. Multivariate logistic regression of cardiotoxicity and patient variables.

Variable	Hormone receptor-negative			Hormone receptor-positive		
	Regression coefficient	P-value	95% CI	Regression coefficient	P-value	95% CI
Cardiotoxicity						
Anthracycline	-5.50	0.018	-10.0, -1.0	0.22	0.800	-1.5, 1.9
Site of cancer	-0.04	0.736	-0.3, 0.2	-0.00	0.990	-0.2, 0.2
Stage	-2.20	0.042	-2.0, 0.0	1.35	0.062	0.1, 2.7
Herceptin cycle >17	2.30	0.160	-0.9, 5.5	-1.20	0.100	-2.7, 0.2
Hypertension	-3.70	0.060	-7.6, 0.2	-1.05	0.290	-3.0, 0.9
Diabetes	-0.60	0.656	-3.2, 2.0	0.45	0.620	-1.4, 2.3

95% CI, 95% confidence interval.

A higher BMI is associated with an increase in risk-related cardiotoxicity in breast cancer patients (34). Our study revealed a significant cardiotoxicity in patients with abnormal body mass index compared to patients with a normal one. Moreover, obesity was linked to worsening cancer outcomes due to underdosing practices in which the dose is not calculated according to ABW. Underdosing for obese patients is practiced to contain the side effects, but the literature review does not support the notion that ABW-based doses cause increased side effects/toxicity (35). According to American Society of Clinical Oncology (ASCO) guidelines, ABW is used for BSA calculation for chemotherapy drug dosing (36,37). However, monoclonal antibodies are administered as a fixed-dose (19). The main reason is the mode of distribution in which monoclonal antibodies distribute via blood plasma and extracellular fluid compartments. An increase in ABW does not directly correlate with an increase in blood plasma and extracellular fluids, and thus, dosing regimens are not formulated according to ABW. Furthermore, clinical trials proved that there is insignificant variation in fixed vs. ABW dosing of monoclonal antibodies by pharmacokinetic analyses owing to a wider therapeutic window of monoclonal antibodies (14). In the French population, obesity has shown no impact on breast cancer prognosis with anthracycline adjuvant chemotherapy (38). Negative effects of obesity are well documented because they alter hemodynamics and thus lead to increased risk of development of cardiovascular disorders and heart failure. However, the susceptibility of breast cancer patients with higher BMI to cardiac disease in response to chemotherapy with anthracyclines has not been adequately investigated.

In the current study, we found that the IBW dose is less than the actual dose. Owing to toxicity concerns, practice pattern studies reported that 40% of obese patients received a reduced chemotherapeutic dose based upon IBW rather than ABW (39). However, the ASCO panel did not find any evidence regarding the rise in short- or long-term toxicities such as myelosuppression in obese patients receiving doses based upon ABW (36). Weight effects can be minimal, and appropriate therapeutics dosage can be calculated while combining weight with other factors (40). Furthermore, pharmacokinetic and pharmacodynamic responses depend upon weight, age, genetics, concurrent diseases, and other factors and can cause interpatient variations (41). Therefore, ASCO's clinical practice guideline for appropriate chemotherapy dosing for obese adult

patients with cancer in 2012 recommends ABW-based dosing for obese patients so that disease-free and overall survival rates are not compromised (36). Similarly, in the current study, we did not find any association of actual dose with cardiotoxicity in breast cancer patients. One of the limitations of our study was small cohort, where we are planning to do a prospective multi-center with a larger patient cohort.

In conclusion, anthracycline and trastuzumab pose adverse cardiac effects that lead to poor outcomes in cancer patients. Saudi patients experiencing significant cardiac toxicity should be considered in the treatment decision, and it may require adherence to use fixed-dose trastuzumab. Higher BMI is associated with an increase in risk-related cardiotoxicity in breast cancer patients. In the current study, the actual dosage was found to differ from the dose based upon ideal body weight. However, there was no association of increased dose based upon actual body weight with cardiotoxicity.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

KAS and NAA designed and developed the study, were responsible for contents, and confirm the authenticity of all the raw data. MA, AAld, AAW, AAli and EFA oversaw data collection, data entry, final review of data and analysis, and were responsible for direction of the study team, and facilitation of the project plan. All authors read and approved the final manuscript.

Ethics approval and consent to participate

All research performed in study involving human participants was in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the Institutional Review Board of King Khalid University Hospital, Riyadh, Kingdom of Saudi Arabia. Written informed consent was obtained from all individual participants included in the present study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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