Trastuzumab-induced cardiac toxicity in breast cancer patients: Identifying key risk factors

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ABSTRACT

Background: Trastuzumab is an effective targeted therapy used for treating human epidermal growth factor receptor 2 (HER2)-positive breast cancer. However, it carries a risk of cardiac toxicity, which can result in heart failure. Identifying patients at high risk of cardiac toxicity is crucial for monitoring and managing their condition.

Aim: This study aims to identify the risk factors associated with cardiac toxicity in breast cancer patients treated with trastuzumab.

Materials and Methods: This retrospective study was conducted at the Military Cancer Center (MCAC) between 2018 and 2020. Data were collected from the medical records of patients. Trastuzumab-induced cardiotoxicity (TIC) was defined based on the Cardiac Review and Evaluation Committee (CREC). Logistic regression determined the association between TIC and the patients' clinical characteristics. Odds ratios (OR) and 95% confidence intervals (CI) were calculated to quantify the strength of the association between TIC and the independent variables. A p-value of less than 0.05 was considered statistically significant.

Results: A total of 292 breast cancer patients were included in the study. Among them, 31 patients (10.6%) developed cardiotoxicity, while 261 patients (89.4%) did not experience any cardiotoxicity. Logistic regression analysis revealed that DM (OR = 3.172, 95% CI: 1.025-9.817, p = 0.045), known history of CAD (OR = 7.156, 95% CI: 1.104-46.384, p = 0.039), hyperlipidemia (OR = 4.960, 95% CI: 1.559-15.788, p = 0.007), and smoking (OR = 3.562, 95% CI: 1.222-10.387, p = 0.020). were all identified as significant independent risk factors for TIC. In all cases, the OR value was greater than 1, and the p-value was less than 0.05.

Conclusion: This study demonstrates that DM, hyperlipidemia, known history of CAD, and smoking, are risk factors for TIC.

Keywords: trastuzumab, cardiac toxicity, breast cancer, risk factors, LVEF.

Introduction

Breast cancer management has undergone a significant transformation with the introduction of HER2-targeted therapies, including trastuzumab, lapatinib, pertuzumab, and ado-trastuzumab emtansine. Overexpression of the HER2 gene is observed in 15-20% of breast cancers and is associated with an aggressive nature, reduced time to recurrence, and decreased survival rates [1],[2],[3].

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The initial phase III clinical trial of trastuzumab conducted in 2001 demonstrated that adding trastuzumab to standard chemotherapy for metastatic breast cancer patients resulted in longer time to disease progression, lower 1-year mortality rates, prolonged survival, and a 20% reduction in the risk of death [2]. However, these trials also highlighted the main adverse event, left ventricular (LV) dysfunction, with an incidence rate of 4-7% during trastuzumab monotherapy, while treatment regimens containing anthracyclines can lead to cardiotoxicity in up to 27% of cases [2],[3],[4].

Unlike anthracycline treatment, the risk of TIC is not dependent on the total dose of the drug and, therefore, is relatively unpredictable. However, it is reversible in most cases, and the drug can be safely reintroduced once the left ventricular ejection fraction (LVEF) has recovered [5]. Therefore, timely identification of patients susceptible to trastuzumab-induced myocardial damage is crucial to prevent the advancement of cardiotoxicity.

MATERIALS AND METHODS

Study Design

This retrospective study was conducted at MCAC. The study period was from 2018 to 2020.

Patient Selection

The study included 339 female patients with HER-2-positive breast cancer treated with trastuzumab. The patients were selected based on their medical records retrieved from the hospital's electronic database. The inclusion criteria comprised: (1) patients who received trastuzumab as part of their treatment regimen; (2) patients who had a normal baseline echocardiogram before initiating trastuzumab; (3) patients who underwent at least one follow-up echocardiogram during trastuzumab treatment; (4) patients aged 18 or older. Those who did not meet these criteria were excluded from the study, as presented in **Table I**.
Specifically, three patients were excluded due to symptomatic heart failure, while the remaining 44 patients were excluded because of incomplete medical records and insufficient follow-up data.

Table I. Patient selection.

Sample size	Patients included	Patients excluded
339	292	47

Data Collection

Data were collected from the patients' medical records, which included information such as age, presence of conventional cardiovascular comorbidities (such as hypertension, DM, hyperlipidemia, known history of CAD, and smoking history), history of radiation therapy, prior use of anthracycline, type of surgery (modified radical mastectomy or WLE), stage of breast cancer classified according to the American Joint Committee on Cancer (AJCC), and the overall duration of trastuzumab therapy.

TIC was defined following the Cardiac Review and Evaluation Committee (CREC) as any of the following: Cardiomyopathy characterized by a reduction in global or severe cardiac LVEF, particularly in the septum; Manifestation of congestive heart failure (CHF) symptoms; Presence of associated CHF signs, including S3

gallop, tachycardia, or both; Symptomatic decline in LVEF exceeding 5%, resulting in an LVEF below 55%, or an asymptomatic decline in LVEF exceeding 10% leading to an LVEF below 55%.

Statistical Analysis

Descriptive statistics were utilized to summarize the patient characteristics. Before logistic regression analysis, the chi-squared test was employed to examine the factors correlated with TIC in a bivariate manner. Variables that achieved a p-value of less than 0.20 were selected for inclusion in the regression analysis for control purposes (Ranganathan, 2017). Logistic regression analysis was then conducted to identify the primary risk factors associated with TIC, with the strength of association measured using an odds ratio. All statistical analyses were performed using IBM Corp.'s Statistical Package for the Social Sciences version 25.0 (Armonk, NY). A p-value below 0.05 was considered statistically significant.

Ethical Considerations

This study is an observational retrospective study conducted within the framework of routine clinical practice. The Institutional Review Board at the Jordanian Royal Medical Services in Amman, Jordan, approved the study protocol.

RESULTS

A total of 292 breast cancer patients were included in the study. Out of these, 31 patients (10.6%) developed cardiotoxicity, while 261 patients (89.4%) did not experience any cardiotoxicity. Regarding age, 58 patients (19.9%) were over 60 years old, and 234 patients (80.1%) were 60 years old or younger. Among the patients, 288 (98.6%) were female, and only 4 (1.4%) were male. Concerning cardiovascular comorbidities, 41 patients (14.0%) had a history of diabetes, while 251 patients (86.0%) did not. Moreover, 54 patients (18.5%) had a history of hypertension (HTN), while 238 patients (81.5%) did not. Only 23 patients (7.9%) had a history of hyperlipidemia, whereas 269 patients (92.1%) did not. Seven patients (2.4%) had a known history of coronary artery disease (CAD), and 285 patients (97.6%) did not.

Smoking was observed in 28 cases (9.6%), while 264 cases (90.4%) were non-smokers. Among the participants, 214 cases (73.3%) had previously undergone anthracycline therapy, whereas 78 cases (26.7%) had not. Radiotherapy was administered to 212 cases (72.6%), while 80 cases (27.4%) did not receive this treatment. Concerning the cancer stage, 36 cases (12.3%) were classified as Stage 1, 88 cases (30.1%) as Stage 2, 110 cases (37.7%) as Stage 3, and 58 cases (19.9%) as Stage 4. The duration of trastuzumab treatment was divided into two groups: 64 cases (21.9%) had a duration of more than 12 months, while 228 cases (78.1%) had a duration of 12 months or less. The type of surgery performed was also recorded: 182 cases (62.3%) underwent MRM, 54 cases (18.5%) had wide local excision (WLE), and 56 cases (19.2%) did not undergo any surgical procedure. Descriptive statistics are presented in **Table II**.

Table II. Descriptive statistics

Variable	Frequency	Percentage
Cardiotoxicity	31	10.6%
No cardiotoxicity	261	89.4%
Age > 60	58	19.9%
Age ≤ 60	234	80.1%
Female	288	98.6%
Male	4	1.4%
DM	41	14.0%
No DM	251	86.0%
HTN	54	18.5%
No HTN	238	81.5%
Hyperlipidemia	23	7.9%
No hyperlipidemia	269	92.1%
Known history of CAD	7	2.4%
No known history CAD	285	97.6%
Smoker	28	9.6%
Non-smoker	264	90.4%
Previous anthracycline therapy	214	73.3%
No previous anthracycline therapy	78	26.7%
Radiotherapy	212	72.6%
No radiotherapy	80	27.4%
Stage 1	36	12.3%
Stage 2	88	30.1%
Stage 3	110	37.7%
Stage 4	58	19.9%
Duration of trastuzumab treatment >12 months	64	21.9%
Duration of trastuzumab treatment ≤ 12 months	228	78.1%
Type of surgery - MRM	182	62.3%
Type of surgery - WLE	54	18.5%
No surgery	56	19.2%

CAD = coronary artery disease, DM= Diabetes mellitus, HTN=Hypertension, WLE = wide local excision, MRM = modified radical mastectomy.

An initial exploratory analysis was conducted using chi-square analysis to identify potential predictor variables associated with TIC. The potential predictor variables considered were age, diabetes mellitus (DM), hypertension (HTN), hyperlipidemia, known history of CAD, smoking history, radiation therapy, previous anthracycline use, cancer stage, and the total duration of trastuzumab therapy.

The results of the chi-square analysis revealed significant associations between TIC and several variables, including DM ($p \leq 0.001$), hypertension (HTN) ($p = 0.037$), hyperlipidemia ($p \leq 0.001$), known history of CAD ($p \leq 0.001$), and smoking history ($p \leq 0.001$). However, no significant associations were found between TIC

and the following risk factors: age, cancer stage, radiation therapy, previous anthracycline use, and the total duration of trastuzumab therapy in months. The detailed results are presented in **Table III**.

Table III. Chi-square analysis

Risk Factor	Trastuzumab induced Cardiotoxicity	No Trastuzumab Induced Cardiotoxicity	Total	P-value
Age in groups				0.176
> 60	9 (15.5%)	49 (85.5%)	58	
≤ 60	22 (9.4%)	212 (90.6%)	234	
DM				0.000
Yes	11 (26.8%)	30 (73.2%)	41	
No	20 (8%)	231 (92%)	251	
HTN				0.037
Yes	10 (18.5%)	44 (81.5%)	54	
No	21 (8.8%)	217 (91.2%)	238	
Hyperlipidemia				0.000
Yes	10 (43.5%)	13 (56.5%)	23	
No	21 (7.8%)	248 (92.2%)	269	
Known history of CAD				0.000
Yes	4 (57.1%)	3(42.9%)	7	
No	27 (9.5%)	258 (90.5%)	285	
Smoker				0.000
Yes	9 (32.1%)	19 (67.9%)	28	
No	22 (8.3%)	242 (91.7%)	264	
Radiotherapy				0.829
Yes	22 (10.4%)	190 (89.6%)	212	
No	9 (11.3%)	71 (88.7%)	80	
Previous anthracycline use				0.066
Yes	27 (12.6%)	187 (87.4%)	214	
No	4 (5.1%)	74 (94.9%)	78	
Total duration of trastuzumab				0.580
>12 months	8 (12.5%)	56 (87.5%)	64	
≤ 12 months	23 (10.1%)	205 (89.9%)	228	
Surgery				0.500
MRM	19 (10.4%)	163 (89.6%)	182	
WLE	4 (7.4%)	50 (92.6%)	54	
No	8 (14.3%)	48 (85.7%)	56	
Stage				0.978
1	4 (11.1%)	32 (88.9%)	36	
2	9 (10.2%)	79 (89.8%)	88	
3	11 (10%)	99 (90%)	110	
4	7 (12.1%)	51 (87.9%)	58	

DM= Diabetes Mellitus, HTN= Hypertension, CAD = coronary artery disease, WLE = wide local excision, MRM = modified radical mastectomy.

Predicting TIC as a function of age, DM, HTN, hyperlipidemia, known history of CAD, smoking status, and previous anthracycline use.

The Chi-square of the binary regression model indicated good model fitness (chi-square = 40.588, p<0.001), which was also confirmed when running Hosmer and Lemeshow Test (p=0.472). Nagelkerke R Square indicated that the model explained 26.5% of the total variance. The model's classification performance can be further understood by examining the confusion matrix. From the confusion matrix, the model accurately predicted a specificity of 98.8% (true negatives) and a sensitivity of 25.8% (true positives). Overall, the model achieved an accuracy of 91%.

The logistic regression analysis demonstrated that several factors were identified as significant independent risk factors for TIC. These factors include DM (OR = 3.172, 95% CI: 1.025-9.817, p = 0.045), known history of CAD (OR = 7.156, 95% CI: 1.104-46.384, p = 0.039), hyperlipidemia (OR = 4.960, 95% CI: 1.559-15.788, p = 0.007), and smoking (OR = 3.562, 95% CI: 1.222-10.387, p = 0.020). No significant associations were found between TIC and the following risk factors: age > 60 (OR = 0.399, 95% CI: 0.089 - 1.784, p = 0.229), HTN (OR = 0.863, 95% CI: 0.218-3.423, p = 0.834), and previous anthracycline use (OR = 2.403, 95% CI: 0.751-7.689, p = 0.140). Detailed results can be found in **Table IV.**

Table IV. Logistic regression analysis

Risk Factor	Odds ratio	95% C.I.	P-value
Age > 60	0.399	0.089 - 1.784	0.229
DM	3.172	1.025 - 9.817	0.045
HTN	0.863	0.218 - 3.423	0.834
Hyperlipidemia	4.960	1.559 – 15.788	0.007
Known history of CAD	7.156	1.104 – 46.384	0.039
Smoking	3.562	1.222 – 10.387	0.020
Previous Anthracycline use	2.403	0.751 – 7.689	0.140

CAD= Coronary artery disease, CI=Confidence Interval. DM= Diabetes Mellitus, HTN= Hypertension. P-value <0.05 was considered statistically significant.

DISCUSSION

A meta-analysis, which compiled data from 17 articles encompassing 6,527 patients, identified diabetes and previous anthracycline use as risk factors for treatment TIC, consistent with our study's findings. In the same analysis, they also recognized older age and hypertension (HTN) as significant risk factors, in contrast to our study [6]. Several published reports have likewise acknowledged advanced age as a noteworthy cardiotoxic risk factor in patients undergoing trastuzumab treatment [6],[7],[8].

The SEER Cancer Statistics Review, published by the National Cancer Institute's Surveillance, Epidemiology, and End Results Program, indicates that the risk of breast cancer increases with age. The report states a 0.4% chance of developing the disease at 30 years old, a 3.6% chance at 60 years old, and approximately 3.8% at 70 years old [9]. In our analysis, the age range of participants spanned from 26 to 83 years, with most studies reporting a cluster of ages between 28 and 80. However, the median age of patients in our study was 51, compared to 63 in previous studies. Furthermore, the national cancer institute reports that female breast cancer is most frequently diagnosed among women aged 65-74, which explains why our study did not identify older age as a risk factor for cardiotoxicity, given the younger age distribution in our population [9].

Importantly, cardiovascular comorbidities such as hypertension (HTN) and diabetes are more prevalent among older patients, and the impact of older age on the incidence of cardiotoxicity tends to overlap with the increased prevalence of major cardiovascular diseases associated with aging. One potential explanation for the findings of our study is that age-related cardiovascular comorbidities, including HTN, atherosclerosis, and diabetes, serve as the primary risk factors for cardiotoxicity rather than age itself. These conditions may be more commonly observed in older individuals, creating the perception that age is a significant risk factor. Nonetheless, although age may not be a direct and independent risk factor for cardiotoxicity, it remains a crucial variable to consider in conjunction with other cardiovascular comorbidities that contribute to the development of cardiotoxicity.

The association between hypertension (HTN), previous anthracycline use, and TIC has been well-established in the literature [10],[11]. Our initial chi-square analysis showed a significant correlation between HTN, previous anthracycline use, and cardiotoxicity. However, a subsequent logistic regression analysis was conducted to investigate this association further. Unexpectedly, the results indicated that HTN and previous anthracycline use did not significantly predict TIC. Future studies should consider larger sample sizes to draw more definitive conclusions about the association between hypertension (HTN), previous anthracycline use, and cardiac toxicity.

It is crucial to acknowledge that TIC is typically reversible with appropriate management, encompassing early detection and timely intervention [12]. Cardiac monitoring during trastuzumab treatment may involve serial echocardiography and clinical assessments. Treatment options for TIC encompass standard heart failure medications such as angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEIs/ARBs) and beta-blockers, as well as newer agents like sacubitril-valsartan and ivabradine [13].

In cases of a significant decline in LVEF, discontinuing trastuzumab therapy may become necessary. However, no defined cutoff point for LVEF decline mandates trastuzumab discontinuation. Nonetheless, the SAFE-HEaRt trial represented the first prospective study to investigate the safety of continuing therapy in asymptomatic patients with LVEF decline ranging from 40% to 49% [14]. The trial's findings support the notion that optimal cancer therapy can be administered to this patient population through collaboration between cardiology and oncology, and decisions regarding the continuation or withholding of trastuzumab treatment should be made on a case-by-case basis.

CONCLUSIONS

While some similarities exist between the Jordanian and the global populations regarding TIC risk factors, the younger age distribution in Jordan distinguishes it from the world population. Therefore, it is crucial to exercise careful monitoring and appropriate management for breast cancer patients in Jordan with DM, hyperlipidemia, prior CAD, and a history of smoking during trastuzumab therapy to mitigate the risk of cardiotoxicity development.

CONFLICT OF INTEREST

None.

FUNDING

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