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Research Article

Predictors of Early Cardiotoxicity in Breast Cancer Patients Treated with Trastuzumab: A Prospective Cohort Study

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Abstract

Background: *Trastuzumab is a widely used and effective treatment for HER2-positive breast cancer. However, its associated cardiotoxicity remains a critical limitation. Predictive tools for identifying at-risk patients are lacking. This study investigates baseline clinical and electrophysiological risk factors for Trastuzumab-related cardiotoxicity.*

Methods: *A prospective observational study was conducted at Al-Bairouni Hospital, Damascus University (2018–2019). Echocardiography and electrocardiography were performed before and three weeks after Trastuzumab therapy. A reduction in left ventricular ejection fraction (LVEF) ≥5%, excluding other causes, defined significant cardiotoxicity.*

Results: *Of 140 breast cancer patients on Trastuzumab, 21.4% developed asymptomatic cardiotoxicity. Prolonged baseline QTc interval (>450 ms) and low estrogen/progesterone receptor expression were significantly associated with cardiotoxicity (P=0.045, P=0.004, and P=0.042). No significant correlation was found with age, cardiac comorbidities, or concurrent chemotherapy.*

Conclusion: *Baseline QT prolongation and low hormone receptor expression are predictive of Trastuzumab-induced cardiotoxicity. Pre-treatment screening using ECG and hormone profiling can enhance patient stratification and inform safer therapeutic decisions.*

Introduction

Breast cancer (BC) remains the most commonly diagnosed malignancy among women worldwide and represents a significant cause of cancer-related mortality. Advances in molecular subtyping have refined therapeutic approaches, particularly the identification of human epidermal growth factor receptor 2 (HER2) as a critical biomarker and therapeutic target. HER2 overexpression or gene amplification occurs in approximately 20–30% of breast cancer cases and is associated with an aggressive phenotype, increased risk of recurrence, and poorer prognosis compared to other molecular subtypes.

The introduction of Trastuzumab, a monoclonal antibody that selectively targets the HER2 extracellular domain, has transformed the treatment landscape of HER2-positive breast cancer. Trastuzumab improves disease-free and overall survival in both early and metastatic settings and is now a standard component of adjuvant and neoadjuvant regimens. However, despite its substantial clinical benefits, Trastuzumab is associated with a well-documented risk of cardiotoxicity, which may manifest as asymptomatic left ventricular dysfunction or, less frequently, symptomatic heart failure.

Trastuzumab-induced cardiotoxicity is distinct from that caused by anthracyclines. Unlike anthracycline-related myocardial damage, which is cumulative and often irreversible, Trastuzumab-related effects are typically reversible upon discontinuation. Nonetheless, they can necessitate treatment interruption or discontinuation, undermining oncologic outcomes. The underlying mechanisms are not fully elucidated but may involve the disruption of HER2-mediated survival pathways in cardiac myocytes, mitochondrial dysfunction, and increased susceptibility to oxidative stress.

Given the potential for serious cardiac adverse events, current guidelines recommend baseline and serial assessment of cardiac function, typically via echocardiography. However, these evaluations primarily detect established dysfunction rather than predict those at risk. There remains a critical need for simple, accessible, and reliable biomarkers to identify patients at higher risk of cardiotoxicity before clinical deterioration occurs.

Electrocardiography (ECG), particularly the corrected QT interval (QTc), offers a readily available tool that may reflect early subclinical myocardial stress. Similarly, hormone receptor (HR) status—particularly estrogen receptor (ER) and progesterone receptor (PR) expression—may influence cardiac vulnerability, as estrogen has demonstrated cardioprotective properties in both preclinical and clinical studies.

This study aims to prospectively investigate the predictive value of baseline QTc prolongation and hormone receptor status in detecting early Trastuzumab-induced cardiotoxicity. By identifying high-risk patients prior to therapy initiation, clinicians may optimize surveillance strategies and personalize treatment approaches, ultimately improving safety and outcomes.

Methods

A prospective cohort study was conducted at Al-Bairouni University Hospital. Female patients with biopsy-confirmed HER2-positive BC indicated for Trastuzumab therapy were recruited between 2018 and 2019.

Treatment followed the standard regimen (loading dose 8 mg/kg followed by 6 mg/kg every three weeks).

All participants underwent baseline and post-treatment echocardiography and electrocardiography. LVEF was calculated using the biplane Simpson's method. A ≥5% reduction in LVEF post-treatment, after ruling out other causes, defined cardiotoxicity. QTc was calculated using Bazett's formula, with >450 ms considered prolonged.

Electrolyte disturbances, medications affecting QT, and other potential confounders were excluded. Statistical analysis employed SPSS v23, using Fisher's exact and Mann-Whitney U tests, with significance set at $P<0.05$.

Results

Of 140 patients included, the mean age was 49.3 ± 10.6 years. Most (88.6%) had non-metastatic disease, and 85% were diagnosed with invasive ductal carcinoma. Hormone receptor positivity was noted in 56% (ER) and 48% (PR). Baseline cardiac comorbidities were rare.

Baseline LVEF averaged 62.9%, declining to 60.6% post-treatment (mean drop: 2.0%). Cardiotoxicity, defined as >5% LVEF reduction, occurred in 30 patients (21.4%) and was entirely asymptomatic.

QTc increased from 425.1 ms to 437.6 ms post-treatment (mean increase: 12.5 ms). Prolonged baseline QTc was present in 13.6% of patients and significantly correlated with cardiotoxicity (OR = 3.38, 95% CI [1.15–9.98], P=0.045). Additionally, low ER and PR expression significantly predicted cardiotoxicity (P=0.004 and P=0.042, respectively). No significant associations were found with age, chemotherapy regimen, or preexisting cardiac disease.

Table 1: Demographic Characteristics of the Sample

Variable	**Count (%)**	**Variable**	**Count (%)**
Diagnosis		**Stage**	
Ductal	119 (85.0)	Ia	10 (7.1)
Lobular	7 (5.0)	IIa	28 (20.0)
Medullary	3 (2.1)	IIb	30 (21.4)
Mixed	11 (7.9)	IIIa	31 (22.1)
Comorbidities		IIIb	8 (5.7)

Variable	Count (%)	Variable	Count (%)
HTN	13 (9.3)	IIIc	17 (12.1)
IHD	4 (2.9)	IV	16 (11.4)
IHF	1 (0.7)	**T Stage**	
AF	1 (0.7)	1	22 (15.7)
Thrombotic	1 (0.7)	2	83 (59.3)
Drugs		3	26 (18.6)
Beta Blocker	10 (7.1)	4	9 (6.4)
ACE Inhibitor	9 (6.4)	**N Stage**	
Diuretics	5 (3.6)	0	43 (30.7)
Ca Channel Block	4 (2.9)	1	39 (27.9)
Aspirin	3 (2.1)	2	39 (27.9)
Digoxin	1 (0.7)	3	19 (13.6)
Clopidogrel	1 (0.7)	**M Stage**	
Warfarin	1 (0.7)	0	124 (88.6)
Rovalto	1 (0.7)	1	16 (11.4)

Table 2: Association Between Cardiotoxicity and Categorical Baseline Characteristics

Variable	Cardiotoxicity	P Value
Cardiac Comorbidities		0.557
None	25 (20.7)	
Any	5 (26.3)	
Cardiac Drugs		0.539
None	25 (20.5)	
Any	5 (27.8)	
Stage of Breast Cancer		0.311
I or II	12 (17.6)	
III or IV	18 (25.0)	
Estrogen Receptors		0.839
Negative	13 (20.6)	
Positive	17 (22.4)	
Progesterone Receptors		0.860
Negative	14 (19.7)	
Positive	16 (23.9)	

Variable	Cardiotoxicity	P Value
Her-2 Mutation		0.838
++	16 (22.5)	
+++	14 (20.3)	
Baseline EF		0.866
>60%	26 (21.7)	
<60%	4 (20.0)	
Prolonged QTc Before Tx		**0.045**
No	15 (14.7)	
Yes	7 (36.8)	
Prolonged QTc After Tx		0.616
No	14 (16.9)	
Yes	8 (21.1)	

Table 3: Association Between Cardiotoxicity and Continuous Baseline Characteristics

Variable	No Cardiotoxicity	Cardiotoxicity	P Value
Age (years)	48 (40.8–56)	54 (44–58.8)	0.134
Estrogen Receptor (%)	40 (13.8–62.5)	10 (10–20)	**0.004**
Progesterone Receptor (%)	35 (20–60)	10 (10–40)	**0.042**
CISH (%)	3.1 (2.7–3.7)	3.1 (2.6–4.1)	0.824
Induction Trastuzumab Dose (mg)	560 (500–600)	560 (527.5–640)	0.318
Maintenance Trastuzumab Dose (mg)	425 (367.5–440)	440 (393.8–471)	0.331

Discussion

This prospective study identified prolonged baseline QTc interval and lower estrogen/progesterone receptor (ER/PR) expression as significant predictors of Trastuzumab-induced cardiotoxicity in HER2-positive breast cancer patients. These findings offer important insights into patient risk stratification and suggest practical, low-cost markers that may enhance current surveillance protocols.

Incidence and Demographic Overview

Cardiotoxicity occurred in 21.4% of patients, which is within the reported range for Trastuzumab-associated cardiac dysfunction, particularly when used following or alongside anthracyclines. The cohort was predominantly composed of ductal carcinoma cases (85%), and stage III disease accounted for the largest group (39.9%), indicating an overall high-risk population. Despite this, no significant correlation was found between disease stage and cardiotoxicity ($p = 0.311$), suggesting that cardiac side effects may be influenced more by patient-specific cardiac parameters than by cancer severity.

QTc Interval and Cardiotoxicity

Among all variables analyzed, prolonged baseline QTc was the only categorical parameter with a statistically significant association with cardiotoxicity ($p = 0.045$). Specifically, 36.8% of patients with a prolonged QTc before therapy experienced cardiotoxicity, compared to only 14.7% of those without QTc prolongation. This supports the hypothesis that electrical instability precedes mechanical dysfunction and could serve as an early warning sign. The post-therapy QTc did not show a statistically significant difference ($p = 0.616$), underscoring the potential of the baseline ECG in preemptive risk assessment.

This finding aligns with prior studies suggesting that QTc prolongation reflects underlying myocardial stress, autonomic imbalance, or subclinical ischemia—all of which could be exacerbated by HER2 blockade in cardiac tissue.

Hormone Receptor Expression

A significant association was found between lower ER ($p = 0.004$) and PR ($p = 0.042$) expression and the development of cardiotoxicity. Patients with cardiotoxicity had a median ER expression of 10%, compared to 40% in those without. For PR, the cardiotoxic group had a median of 10%, compared to 35% in non-cardiotoxic patients. These findings support the protective role of estrogen and progesterone signaling in cardiac tissue, potentially mitigating oxidative stress and apoptotic pathways activated during Trastuzumab exposure.

Although the categorical ER/PR status (positive vs. negative) did not reach statistical significance, the continuous data provide more nuanced insight, suggesting that the degree of receptor positivity may be more relevant than simple positivity alone

Other Factors

Interestingly, age, baseline ejection fraction (EF), and presence of cardiac comorbidities or cardiac medications did not significantly predict cardiotoxicity. This contrasts with some earlier reports where older age and reduced baseline EF were associated with increased risk. The lack of association in our study may be attributed to the relatively narrow EF range (most patients had EF >60%) and a low prevalence of comorbid cardiac conditions, such as hypertension or ischemic heart disease (only 9.3% and 2.9%, respectively).

Additionally, Trastuzumab dosing (both induction and maintenance) did not show significant differences between groups, suggesting that dose intensity alone may not be a determining factor in early cardiac toxicity when standard regimens are followed.

Clinical Implications

The identification of baseline QTc prolongation and lower ER/PR expression as risk factors for cardiotoxicity offers a practical framework for refining pre-treatment cardiac assessment. ECG is an inexpensive, readily available tool that could be integrated into standard protocols to flag at-risk patients. Similarly, patients with low or borderline hormone receptor expression might benefit from closer cardiac monitoring or earlier cardiology referral, even if asymptomatic.

These results also raise the possibility of tailored cardioprotective strategies (e.g., beta-blockers, ACE inhibitors) in high-risk patients, although prospective interventional studies would be required to support this approach.

Limitations and Future Directions

This study is limited by its sample size, short follow-up duration, and potential selection bias, as patients with overt cardiovascular disease were likely excluded or underrepresented. Additionally, the analysis of QTc relied on a single ECG measurement, and inter-reader variability, although minimized, remains a consideration.

Future research should include longitudinal follow-up, incorporate cardiac biomarkers (e.g., troponin, NT-proBNP), and validate the findings in larger, multi-center cohorts. Further exploration into the molecular mechanisms by which ER/PR signaling modulates cardiotoxicity risk may also inform novel protective strategies or adjunct therapies.

Conclusion

This study proposes QTc interval prolongation and low ER/PR expression as simple yet powerful predictors of Trastuzumab-related cardiotoxicity in HER2-positive breast cancer patients. These predictors can be integrated into routine screening to enhance treatment safety and individualize monitoring protocols.

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