Individuals deemed low risk for cardiotoxicity with HER2-directed antibody therapy developed modest incidences of treatment-related LVEF decline and heart failure across a large, Western US hospital system

Cameron Smith[1], David Page[1], Michael Layoun[2], Hsin-Fang Li[3], Erin Koltner[3], Mary T. Imboden[3], Zachary Taylor[2], Kateri J. Spinelli[3]

1 Providence Cancer Institute, Providence Portland Medical Center, Portland, OR , 2 Providence Heart Institute, Providence Portland Medical Center, Portland, OR , 3 Center for Cardiovascular Analytics, Research and Data Science, Providence Heart Institute, Providence St Vincent Medical Center, Portland, OR

Background

- Incidence of anti-HER2 cardiotoxicity varies widely from 3-30%.
- Baseline cardiac risk factors can drastically affect an individual's risk of cardiotoxicity while on anti-HER2 therapies.
- Risk stratification calculators like the HFA-ICOS tool can estimate relative risk of cardiotoxicity based on preceding risk factors.
  - High risk factors: Heart failure (HF), CAD, severe valvular heart disease
  - Mild-moderate risk factors: HTN, DM, CKD, age 65-79, anthracycline use, arrhythmia, smoking history, BMI>30
- De-intensified surveillance has been proposed for low-risk patients.

Objective

- Characterize incidence and predictors of cardiotoxicity in a real-world population of early-stage breast cancer patients receiving anti-HER2 therapies.
- Evaluate incidence of cardiotoxicity among low-risk cohorts.

Methods

- Retrospective cohort study of n=1,156 early stage (I-III) breast cancer patients who received anti-HER2 therapy and completed baseline and surveillance echocardiography in the 7-state Providence healthcare network between 1/1/2016-3/20/2024.
- Primary outcome: Development of LVEF ≤50% during anti-HER2.
- Secondary outcomes: New clinical heart failure (HF) diagnosis, any hospitalization, and all-cause mortality.
- LVEF ≤50% and new HF % were also obtained in low-risk cohorts:
  - Group 1 (not high risk): No prior HF, CAD, anthracycline use
  - Group 2 (low-risk): One mild-moderate cardiac risk factor
  - Group 3 (no-risk): No preceding cardiac risk factor
- Logistic regression models accounting for demographics, comorbidities, HER2 regimen, and preceding cardiac medications were performed.

Results

Table 1. Baseline characteristics among breast cancer patients receiving HER2-therapy

	All Patients (N=1,156)	Preserved LVEF Subgroup (N=1,104)	LVEF ≤50% Subgroup (N=52)	P-value
Age*	56.4 (12.6)	56.4 (12.6)	56.7 (12.3)	0.8841
Female, N (%)	1149 (99%)	1099 (100%)	50 (96%)	0.0266
Race*, White, N (%)	849 (73%)	807 (75%)	42 (84%)	0.0227
Ethnicity*, Hispanic, N (%)	115 (10%)	111 (10%)	4 (8%)	0.8126
BMI*, ≥40	94 (8%)	87 (8%)	7 (13%)	0.0977
Baseline comorbidities*, N (%)				
Hypertension	329 (28%)	314 (28%)	15 (29%)	1
Hypercholesterolemia	399 (35%)	381 (35%)	18 (35%)	1
Diabetes	134 (12%)	126 (11%)	8 (15%)	0.5140
Smoking status (% current or former smokers)	72 (6%)	68 (6%)	4 (8%)	0.6582
Coronary artery disease	**46 (4%)**	40 (4%)	**6 (12%)**	**0.0145**
Heart failure	**30 (3%)**	**26 (3%)**	**4 (8%)**	**0.0419**
Atrial fibrillation	37 (3%)	34 (3%)	3 (6%)	0.2296
Cerebrovascular disease	49 (3%)	46 (4%)	3 (6%)	0.4803
Referral to cardiology prior to treatment	40 (3%)	37 (3%)	3 (6%)	0.4202
Cardiac meds prior to HER2*	265 (23%)	23 (2%)	15 (29%)	0.3116
HER2 treatment group*				**0.0001**
Taxane + anthracycline-containing regimens	**94 (8%)**	82 (8%)	**12 (24%)**	
Taxane + platinum-containing regimens	572 (51%)	**555 (52%)**	17 (33%)	
Taxane only regimens	448 (40%)	426 (40%)	22 (43%)	

Data presented as n (%) or mean (SD) | *Variables included in the multivariate model; Items that are statistically significant are indicated in bold.

- 4% of patients (n=52) developed LVEF ≤50% during anti-HER2 therapy.
- Univariate modeling revealed that baseline coronary artery disease (aOR [95% CI] = 3.22 [1.21, 8.61]) and prior heart failure (aOR [95% CI] = 3.67 [1.23-10.99]) were associated with treatment-related LVEF ≤50%.
- Compared to taxane-only regimens, the use of anthracyclines was significantly associated with LVEF ≤50% on multivariate analysis (aOR [95% CI] = 3.6 [1.5, 8.1]).
- New HF diagnoses were observed in 11% of patients receiving anthracyclines compared to 4-5% of patients in other treatment arms (p = 0.024).

Table 2. Patient outcomes while on HER2 therapy

	All Patients (N=1,156)	LVEF ≤50% Subgroup (N=52)
Decline in LVEF, average	-5.3 (2.9)	-8.7 (3.8)
Referral to cardiology while on treatment	31 (3%)	8 (15%)
Cardioprotective meds after start of HER2	111 (10%)	19 (37%)
New HF diagnosis	65 (6%)	22 (42%)
ED and hospital encounters	458 (40%)	27 (52%)
Mortality	0 (0%)	0 (0%)

Data presented as n (%), mean (SD), or range

- Only 15% of patients with LVEF decline related to anti-HER2 therapy were referred to cardiology, and less than half were initiated on cardioprotective medications.

Table 3. Incidence of cardiotoxicity among low-risk cohorts

Low-Risk Cohort	Number of Patients	LVEF ≤50%	HF %
Group 1: Not-high risk	968	3.4%	2.7%
Group 2: Low-risk	293	5.8%	4.1%
Group 3: No risk	80	0%	2.5%*

*The two patients with ICD-10 diagnosis of HF in the no-risk cohort did not have any clinical symptoms and never required cardioprotective therapy

- Most low-risk individuals (Group 1 + 2) still developed modest incidences of LVEF ≤50% and new clinical heart failure.
- Individuals without any preceding cardiac risk factors had zero cases of treatment-related LVEF ≤50% during surveillance.

Conclusions

- In a real-world clinical setting, anti-HER2-associated LVEF declines were uncommon but were associated with increased hospitalizations and clinical heart failure.
- Baseline coronary artery disease, prior heart failure, and exposure to anthracyclines were associated with higher rates of anti-HER2-associated LVEF decline.
- Interim analysis of low-risk cohorts demonstrated modest incidences of LVEF decline and HF, supporting the practice of continued echo surveillance in these subgroups.
- The cohort with zero cardiac risk factors had no cases of treatment-related LVEF decline or clinically significant heart failure, suggesting that deferred echo surveillance could be considered in this population.

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Contact info: Cameron Smith, DO, MPH; Disclosures: None

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