Late Anthracycline-Related Cardiotoxicity in Low-Risk Breast Cancer Patients

Anthracyclines improve survival in breast cancer, but can cause cardiotoxicity, manifest either as overt clinical heart failure or asymptomatic left ventricular dysfunction. Determining cardiotoxicity prevalence is difficult; definitions vary, presentation may be delayed, and risk varies by chemotherapy regime and dose, and with cardiovascular comorbidities. Guidance regarding the optimal frequency and duration of long-term monitoring for cardiovascular toxicity is, therefore, lacking.

We sought to assess late anthracycline cardiotoxicity in low-risk breast cancer survivors receiving standard anthracyclines, using multimodality imaging: cardiovascular MR imaging for left ventricular volume, ejection fraction (LVEF), tissue characterization including fibrosis quantification, and advanced echocardiography for early cardiac dysfunction.

Subjects recruited to a previous study of early anthracycline cardiotoxicity, the BETTER-CARE study (BC) (1), were invited to participate. This study investigated cardiotoxicity pathogenesis in patients with no prior cancer history, free from pre-existing cardiovascular risk factors or disease, treated for early stage breast cancer, and all patients underwent standard CMR imaging before chemotherapy, including late gadolinium enhancement imaging. Investigations at follow-up included repeat cardiac MR (with sequences standardized with the baseline scan), additional acquisition of modified Look Locker inversion recovery T1 maps to generate extracellular volume maps using blood hematocrit (2), echocardiography (tissue Doppler and speckle tracking-derived strain measures), as well as blood biomarkers. Clinical outcomes were obtained from electronic patient records and patient questionnaires, and from death certificates. Female healthy volunteers (HV) of similar age were recruited for comparison (n ¼ 34). Research had appropriate ethical approvals and written informed consent. Between-group comparisons were undertaken using the Student t test for continuous variables, and by chi-square or Fisher exact test for categorical variables.

Of the 166 original BC participants, 25 (15%) had cancer recurrence/metastases (10 deaths). Two subjects died from noncardiovascular, nononcological causes. Ninety-eight subjects (mean age: 55.0 ± 8.5 years) underwent follow-up imaging at a mean of 6.0± 1.2 years after the first anthracycline dose. Anthracycline doses were considerably below levels considered high risk; the mean cumulative epirubicin dose was 399±85 mg/m2. Twenty-five percent of subjects also received trastuzumab, 73% hormonal therapy, and 84% radiotherapy (51% left sided/whole chest).

At follow-up, all patients were free from cardiovascular symptoms and signs. None had ever received a heart failure diagnosis. Overall, absolute LVEF decreased by a mean of 3.7±4.2% (range: -13% to 8%), with reductions of 10% or more in 8 subjects. However, because LVEF remained >55% in all, none met criteria for cancer therapy-related cardiac dysfunction (3). Reductions in the LVEF were no greater in subjects exposed to radiotherapy or trastuzumab, although those receiving higher anthracycline doses (>450 mg/m2 of epirubicin) had greater interval change (-4.6 ±3.7% vs. -2.7±4.4%; p ¼ 0.030) (Figure 1). Left ventricular volumes, mass, and LVEF were similar in HV and BC subjects at follow-up, and no subjects had a significant scar on late enhancement imaging.

Myocardial septal extracellular volume was similar between groups (BC vs. HV: 0.28 ± 0.028 vs. 0.28 ± 0.029; p 0.803); however, native myocardial T1 was marginally higher in the BC group compared to the HV (1,052 _ 30 ms vs. 1,037 _ 31 ms; p ¼ 0.012). Compared with HV, the BC cohort had slightly worse tissue Doppler indices of function and global longitudinal and radial strain, and higher values of N-terminal pro–B-type natriuretic peptide (9.97 ± 1.93 pmol/l vs. 7.32 ± 1.90 pmol/l; p 0.024), but again, all values fell within normal ranges.

Using multimodality technologies in a low-risk population followed for 6 years, standard anthracycline chemotherapy caused no clinically significant cardiotoxic effects (no cardiovascular deaths, heart failure events, or decreases in function sufficient to meet cancer therapy-related cardiac dysfunction criteria). There were small, dose-related changes in cardiac function when compared with HV, but these modest cardiac changes compare with 15% cancer recurrence, including 6% who died. This is an imbalance; in low-

risk patients, the risk of late cardiotoxicity seems to be small compared with tumor recurrence and progression risk.

Most previous anthracycline cardiotoxicity studies used short follow-up, and assume that function decreases linearly with time. Early (2-year) assessments of cardiotoxicity in the complete BC cohort found frequent subtle changes in LVEF (LVEF reductions $5% in 21% of subjects) (1); however, these current results are reassuring and align with previous evidence following 2625 subjects for more than 5 years, where 98% of cardiotoxicity occurred in the first year (4). Allowing for potential survival bias (follow-up of the complete baseline cohort was impossible), these findings support focusing screening on early detection of cardiotoxicity, with late follow-up confined to high-risk groups.

CMR	BC (n=98)	HV* (n=34)	P value
LVEDV-1, ml/m^2	66±8	66±10	0.792
LVESV-1, ml/m^2	21±4	21±5	0.821
LVEF, %	68±5	68±4	0.414
Native myocardial T1, ms	1052±30	1037±31	0.012
ECV	0.28±0.028	0.28±0.029	0.803
Echocardiography	BC (n=93)	ECHOHV* (n=33)	
Mean E' tissue Doppler velocity, m/s	0.11±0.02	0.12±0.03	0.009
E/E' ratio	6.11±1.56	6.32±1.79	0.52
GLS, %	-22.2±1.80	-23.3±1.46	0.002
GRS, %	39.2±13.7	50.0±11.8	<0.001

Figure 1: The BETTER-CARE (BC) Study recruited 166 breast cancer subjects at low cardiovascular risk receiving anthracycline chemotherapy, all of whom underwent cardiac magnetic resonance (CMR)) at baseline before chemotherapy. Six years later, 98 subjects underwent comprehensive cardiovascular follow-up including CMR, T1 mapping, advanced echocardiography, and blood biomarkers. There were small (but detectable) differences between some imaging parameters in BC subjects and healthy controls. AC – anthracycline dose; ECHOLV- echo healthy volunteers; ECV- extracorporeal volume; GLS- global longitudinal strain; GRS- global radial strain; HV- healthy volunteers; LVEDV- left ventricular end-diastolic volume; LVEF left ventricular ejection fraction; LVESV- left ventricular end-systolic volume.

*CMR healthy volunteer (HV) and echo healthy volunteer (ECHOHV) differed.

Clinical outcomes at 6 years following anthracycline chemotherapy: Cancer (25 recurrence, 10 deaths), cardiovascular (0 heart failure events, 0 deaths).

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