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Letter to the editor

A post-hoc subgroup analysis assessing acute cardiac biomarker profiles in female cancer patients during adjuvant therapy

Dear editor:

With advancements in the efficacy of therapies for cancer patients, the number of long-term cancer survivors is increasing [1]. However, some anticancer therapies carry some risk of treatment-induced cardiovascular disease and heart failure if cardiotoxic systemic therapies and radiotherapy adjacent to the heart are a part of the patient's treatment regimen [2]. Asymptomatic cardiac toxicity may remain undetected with conventional diagnostic imaging tools, resulting in a delayed diagnosis and progression of cardiovascular disease [1]. Alternate diagnostic tools such as clinical chemistry assays, may be important for early detection of cardiac complications from anticancer therapies to prevent severe and irreparable heart damage. To that end, recommendations for sex-specific cutoffs, especially for high-sensitivity cardiac troponin (hs-cTn) assays, are proposed as population-based studies have demonstrated lower concentrations of hs-cTn in healthy women [3]. Thus, our objective was to assess the early temporal relationship of cardiac injury biomarkers between different potentially cardiotoxic adjuvant-therapies in female cancer patients.

A post-hoc subgroup analysis was conducted focusing only on women from the MEDICATE (MEDiastinal Irradiation and CArdioToxic Effects) study, which involved predominantly Hodgkin's and non-Hodgkin's lymphoma patients who received mediastinal radiotherapy (RT) after anthracycline chemotherapy, and the CABOT (Cardiac Biomarkers on Trastuzumab: Determining the cardiac biomarker profile in breast cancer patients receiving adjuvant trastuzumab therapy), study which involved HER2 positive breast cancer patients who received adjuvant trastuzumab therapy (both studies received ethics approval) [4–6]. Blood (serum for MEDICATE and EDTA plasma for CABOT) was collected (MEDICATE, 0, 2, 4 weeks into RT and CABOT 0, 3, 6 weeks on trastuzumab) and stored (< -70 °C). The study cohort included only those women with all three blood collections and was further stratified into three groups: i) lymphoma patients receiving mediastinal RT (n = 4); ii) breast cancer patients treated with adjuvant trastuzumab without RT during this timeframe (n = 16); and iii) breast cancer patients treated with adjuvant trastuzumab and RT (n = 5). All samples were tested for heart-type fatty acid binding protein (H-FABP, Randox) and hs-cTnI (Abbott), with stability and analytical performance previously established [7,8]. Left ventricular ejection fraction (LVEF) was assessed at 3 months (CABOT) and 12 months (MEDICATE). Differences in assay measurements between timepoints were assessed visually and descriptively with non-parametric analyses as well as using the upper limit of normal (ULN) for the respective biomarkers (H-FABP 99th = 6.3 μg/l and Abbott female hs-cTnI 99th = 16 ng/l) to assess prevalence of myocardial injury [7,9].

Baseline demographics and disease characteristics are summarized in Table 1. All patients received chemotherapy prior to the commencement of radiation or trastuzumab therapy, with all MEDICATE and 20 of 21 CABOT patients having received an anthracycline. For MEDICATE, all patients had two-field radiotherapy using an anterior-posterior beam arrangement, whereas for CABOT, 2 of the RT patients received radiation to the left side chest wall or breast, and 3 received radiation to the right side.

In MEDICATE there was 1 patient with H-FABP > ULN and 3 patients with hs-cTnI > ULN using accepted cutoffs for myocardial injury at any timepoint. In CABOT (without RT) there was 1 patient with H-FABP > ULN, and all 16 patients with hs-cTnI > ULN. Among patients who received radiotherapy in CABOT, 3 of the 5 patients had hs-cTnI > ULN. Notably, for patients who did not receive RT, the change in median hs-cTnI concentration went from 19 ng/l at baseline to 65 ng/l at 3 weeks, followed by a drop to 25 ng/l at 6 weeks for (p = .001, Friedman test via MedCalc software) (Fig. 1).

After 1 year, all MEDICATE patients had LVEF > 50% (LVEF median = 56%, range: 55–59; n = 4). However in CABOT, after 3 months on trastuzumab therapy, (LVEF median (no RT) = 58%, range: 42–67%; n = 16 and LVEF median (RT) = 60%, range: 52–66%; n = 5), 2 patients discontinued treatment due to cardiotoxicity and 1 patient had a LVEF of 45% but remained on treatment. These 3 patients did not receive RT. One patient who discontinued trastuzumab treatment had persistently elevated hs-cTnI (before 1st treatment = 115 ng/l, before 2nd treatment = 128 ng/l, before 3rd treatment = 66 ng/l) and H-FABP (16, 17, and 22 μg/l) at all 3 timepoints. In contrast, the other CABOT patient who discontinued trastuzumab treatment had hs-cTnI slightly above the ULN only at the first timepoint (21, 10, and 6 ng/l), with undetectable H-FABP concentrations at all timepoints. The third patient who experienced cardiotoxicity (but remained on trastuzumab) had hs-cTnI slightly elevated during the third timepoint (5, 12, and 19 ng/l) with H-FABP < ULN (2 μg/l at all timepoints).

In this post-hoc analysis of women undergoing adjuvant treatment for cancer, employing the female sex-specific 99th percentile cutoff for hs-cTnI identified > 85% of women with myocardial injury at one timepoint during the study timeframe. Collectively, only 3 women experienced early cardiotoxicity or a significant decline in LVEF, yet 22 of these 25 women had myocardial injury, suggesting that additional variables (besides an elevated hs-cTnI concentration) may need to be considered when assessing which women are at risk for cardiotoxicity early after adjuvant treatment. This is not unique to the Abbott hs-cTnI assay, as the Beckman hs-cTnI assay yielded a similar biochemical profile with the highest hs-cTnI concentrations also observed at 3 weeks in the CABOT study [6]. With only 2 patients having H-FABP above the ULN (1 of which experienced cardiotoxicity), measuring this biomarker could be beneficial in identifying myocardial injury.

One confounding variable in this analysis is the use of anthracyclines, which is known to be a dose-dependent cardiotoxic agent [10]. Nearly all patients in both studies had doxorubicin as part of their chemotherapy regimen. Following chemotherapy, the median hs-cTnI

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Table 1
Demographics of MEDICATE and CABOT study cohorts.

Variable	MEDICATE mediastinal radiotherapy (RT) (n = 4)	CABOT trastuzumab + RT (n = 5)	CABOT trastuzumab (n = 16)
Median Age (range), years	27 (20-42)	49 (42-66)	54 (36-68)
Cancer diagnosis			
Diffuse Large B-cell Lymphoma	2		
Hodgkin's Lymphoma	2		
Invasive Ductal Carcinoma		5	16
Invasive Lobular Carcinoma		0	1 (1 patient with both)
Location of Cancer			
Mediastinum	4		
Left breast		2	7
Right breast		3	8
Bilateral breast cancer			1
Systemic therapy			
R-CHOP[1]	2		
ABVD[2]	2		
AC[3]		1	0
AC-T[4]		3	15
FEC-D[5]		0	1
DC[6]		1	0
Trastuzumab	0	5	16
Endocrine therapy	0	2	0
Radiation therapy			
3500 cGy/20 fractions(#)	3		0
3060 cGy/17#	1		
4256 cGy /16#		2 (1 boost 1000cGy/5)	
5000 cGy /25#		3 (1 boost 1000cGy/5)	

[1]Rituximab, Cyclophosphamide, Doxorubicin Hydrochloride, Vincristine Sulfate, Prednisone (R-CHOP), [2]Adriamycin (Doxorubicin), Bleomycin, Vinblastine, Dacarbazine (ABVD), [3]Doxorubicin, Cyclophosphamide (AC), [4]Doxorubicin, Cyclophosphamide, Paclitaxel (AC-T), [5]Fluorourcil/ Epirubicin, Cyclophosphamide, Doxetaxel (FEC-D), [6]Docetaxel, Cyclophosphamide (DC).

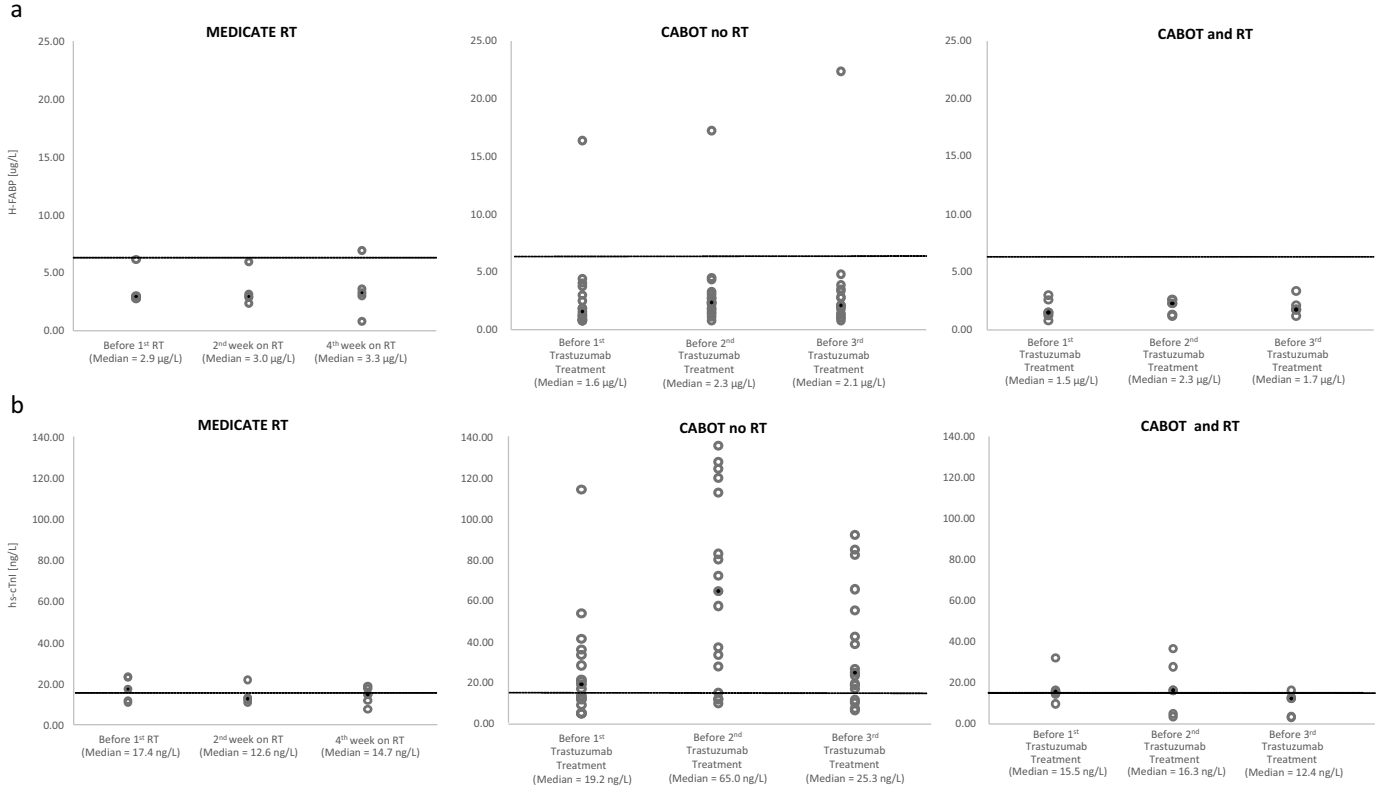

Fig. 1. Cardiac injury biomarker concentrations at all 3 time points in the MEDICATE and CABOT study cohorts for H-FABP (a) and hs-cTnI (b). Note: the solid black circle represents the median concentration of the respective biomarker in the 3 groups.

concentrations at baseline before adjuvant treatment was ≥16 ng/l in all 3 groups. However, despite this biochemical indication of injury prior to commencement of the adjuvant therapy, no patient had a LVEF < 50% nor exhibited signs related to cardiotoxicity. Additional limitations are that the therapies employed were not uniform in these analyses; nor do we have post 1 year follow-up from these populations to further assess long-term cardiac outcomes. Nevertheless, despite the small sample size, post-hoc design, and different cancer populations, these data suggest that hs-cTnI measurements alone and interpreted using the sex-specific 99th percentile may not be the most optimal way to detect early cardiotoxicity in female patients undergoing adjuvant therapy. Specifically, to establish evolving myocardial injury on treatment it may be important to obtain baseline hs-cTn concentrations before the administration of potential cardiotoxic drugs, as minor changes in concentrations outside this setting have important prognostic implications **[11,12]**. Finally, additional studies assessing different hs-cTn cutoffs and possibly a combination of biomarkers may be helpful in predicting subsequent treatment-related cardiotoxicity over both the short and long-term in female cancer patients.

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Conflict of interest/disclosures

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