High-Sensitivity Troponin T and NT-proBNP Kinetics in Breast Cancer Chemotherapy

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Keywords

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Abstract

Background/Aims: Doxorubicin (DOX) and trastuzumab (TRA) are associated with cardiac dysfunction. **Method:** High-sensitivity troponin T (hs-TnT) and brain natriuretic peptide attached to the amino acid N-terminal fragment in the prohormone (NT-proBNP) were measured before and on days +1, +2, +3, and +7 during cycles 1 and 2 of therapy with DOX or TRA in breast cancer patients. **Results:** Five of eleven DOX-treated women, compared with 2/11 TRA-treated women, had undetectable baseline hs-TnT. By day +1 of cycle 2, all the DOX-treated women ($p = 0.03$) but only 7/11 TRA-treated women ($p = \text{ns}$) had detectible hs-TnT. Time to peak was 1–2 days for both groups. In the DOX-treated women, hs-TnT showed significant peaks from precycle baseline, increases in precycle 1 to precycle 2 levels, and a cycle 1 to

cycle 2 peak and area under the curve (AUC). hs-TnT increased from precycle (1, 4.6 ± 6.3 pg/mL) to a cycle 2 peak of 16.1 ± 15.0 pg/mL ($p < 0.002$). No increases were seen with the TRA treatment. Transient posttreatment increases in NT-proBNP were seen after both therapies. **Conclusion:** DOX was associated with increased pretreatment baseline, peak, and AUC hs-TnT levels. Both DOX and TRA acutely perturb NT-proBNP. Assessment of pre- and posttreatment hs-TnT could be a means of quantifying cumulative myocardial injury in the course of chemotherapy.

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Introduction

Doxorubicin (DOX) and trastuzumab (TRA) are widely used in the treatment of breast cancer and are associated with the development of cardiac dysfunction. There is a need to identify patients who are at a high risk of developing cardiac complications from these agents, and monitoring during treatment could allow modifications designed to minimize cardiac dysfunction [1, 2]. Current monitoring, with ejection fraction (EF), lacks the

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Table 1. Baseline characteristics of patients in the doxorubicin group

Patient No.	Age, years	Breast cancer stage	ER/PR/HER2 status of tumor	Adjuvant radiation/side	LVEF at baseline, %	LVEF at 3/6/9/12 months, %	Total DOX doses, <i>n</i>	Development of CHF
1	50	III	+/+/-	yes/left	60	-/-/65/-	4	no
2	48	II	-/-/-	yes/left	61	-/-/-/-	4	no
3	47	II	+/+/-	no	57	47/53/-/51	4	yes
4 ^a	48	II	+/+/+	yes/right	56	56/53/52/50	4	no
5	71	II	+/-/-	yes/left	65	-/-/-/-	4	no
6	43	III	+/+/-	yes/right	68	56/-/-/-	4	no
7	50	II	+/+/-	yes/left	62	-/-/-/-	4	no
8	59	III	+/+/-	yes	67	-/-/-/-	4	no
9	52	II	-/-/-	yes	64	63/-/-/-	4	no
10	58	III	-/-/+	yes/right	57	60/58/56/60	4	no
11	63	II	+/+/-	yes/left	63	67/-/60/-	4	no

DOX, doxorubicin; LVEF, left ventricular ejection fraction; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal receptor2; CHF, congestive heart failure.

^a This patient had previously received 25 doses of trastuzumab.

sensitivity to detect early subclinical changes or predict subsequent declines in function with treatment [2]. Cardiac biomarkers such as troponins, brain natriuretic peptide attached to the amino acid N-terminal fragment in the prohormone (NT-proBNP), and myeloperoxidase have been explored as potential means of early identification of chemotherapy-induced cardiac toxicity in vulnerable patients [3–5]. The conventional troponin T (TnT) assay performs well for discriminating noncardiac chest pain from myocardial infarction, but its imprecision at low values makes the detection of subclinical myocardial damage unreliable. High-sensitivity (hs)-TnT assays overcome this limitation. However, the kinetics early after chemotherapy remain undefined [6, 7]. A new hs-TnT assay (Roche Diagnostics, Indianapolis, IN, USA) had a detection limit of 3 pg/mL pre-US FDA approval during testing. The post-US FDA approval detection limit is 6 pg/mL, and 99th percentile threshold for women is 14 pg/mL. The objective of our pilot study was to evaluate the kinetics of hs-TnT in comparison to a widely used biomarker, NT-proBNP, during the first and second cycles of treatment with DOX or TRA in breast cancer patients.

Methods

We studied hs-TnT and NT-proBNP levels just before (at baseline), and on days +1, +2, +3, and +7 during the first and second cycles in women with stage I–III breast cancer treated with adjuvant or neoadjuvant DOX (administered as dose-dense) or TRA.

Cardiac imaging was performed as per usual clinical care, usually prior to treatment, and then either at 3, 6, or 12 months. The characteristics of hs-TnT differ from the conventional assay [8]. In this protocol, blood was collected in serum tubes, centrifuged, and stored frozen at –80°C. Each sample had a single freeze/thaw cycle. All laboratory analyses were conducted blinded to clinical status. NT-proBNP (detection limit: 5 pg/mL) was performed on a Cobas e601 automated immunoassay analyzer using the Elecsys proBNP II assay. hs-TnT measurement was performed on a Cobas E601 automated immunoassay analyzer using the Elecsys TnT hs assay (Roche Diagnostics). This assay as tested had a limit of detection of 3 pg/mL, and the 99th percentile cutoff in a healthy population is 14 pg/mL. Mean and standard deviation are presented. Calculated kinetic variables included baseline and peak values, time to peak, and baseline-corrected area under the curve (AUC). In calculating the AUC, missing values for DOX (7/55 samples) and TRA (1/55 samples), were imputed from the last known value, and values below the hs-TnT detection limit, were assigned a value of 2 pg/mL. The pretreatment to posttreatment continuous variables were analyzed statistically by the *t* test. Nonparametric comparisons were assessed with the Fisher exact test. *p* < 0.05 was considered the threshold for statistical significance.

Results

Median ages were 51 years (DOX group, *n* = 11; Table 1) and 60 years (TRA, *n* = 11; Table 2) years. Left ventricular EF was normal at baseline in women treated with DOX (63 ± 4%) and TRA (64 ± 4%). Four women in the TRA group had received DOX prior to study enrollment. One woman in the TRA group received concurrent

Table 2. Baseline characteristics of patients in the trastuzumab group

Patient No.	Age, years	Breast cancer stage	ER/PR/HER2 status of tumor	Adjuvant radiation/side	LVEF at baseline, %	LVEF at 3/6/9/12 months, %	Total TRA doses, <i>n</i>	Development of CHF
1	80	I	+/-/+	yes/right	57	55/63/63/56	25	no
2	64	III	-/-/+	yes/right	55	66/62/60/67	25 ^a	no
3	64	I	+/+/+	Yes/right	62	62/63/60/64	19 ^b	no
4	41	III	+/-/+	yes/right	67	74/58/63/62	25 ^a	no
5	75	III	-/-/+	yes/right	56	55/59	25 ^a	no
6	79	I	+/+/+	yes/right	66	61/62/68/67	25	no
7	64	III	-/-/+	yes/left	66	63/65/61/69	25 ^a	no
8	61	III	+/-/+	yes/right	67	64/56/63/63	25	no
9	45	II	+/+/+	no	69	-/67/72	25	no
10	54	I	-/-/+	no	64	-/65/73	25	no
11	48	I	-/+/+	yes/left	64	-/64/65	25	no

TRA, trastuzumab; LVEF, left ventricular ejection fraction; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal receptor 2; CHF, congestive heart failure.

^a Patients also previously received doxorubicin. ^b TCH (taxotere, carboplatin, herceptin) chemotherapy.

Table 3. Mean values of hs-TnT and NT-proBNP for doxorubicin and trastuzumab

	DOX, cycle 1	DOX, cycle 2	<i>p</i> value	TRA, cycle 1	TRA cycle 2	<i>p</i> value
hs-TnT						
At baseline, ng/mL	4.6	9.3	<0.002	7.7	5.0	ns
Peak, ng/mL	9.6**	16.1 [†]	<0.002	8.0	6.8	ns
Time to peak, days	1.6	1.5	ns	1.1	1.3	ns
AUC above baseline	7.1±13.4	27±19	<0.001	-1.4±7.2	-5±17	ns
NT-proBNP						
At baseline, pg/mL	94	90	ns	124	80	ns
Peak, pg/mL	361*	359*	ns	209	206 [†]	ns
Time to peak, days	1.8	1.9	ns	2.2	1.8	ns
AUC above baseline	423	499	ns	78**	-32**	<0.5

DOX, doxorubicin; TRA, trastuzumab. * $p < 0.001$; [†] $p \leq 0.01$; ** $p < 0.03$; ^{††} $p = 0.002$; ns, $p > 0.05$.

docetaxel and carboplatin. Their data were included in the assessment of the acute, short-term response to TRA. Baseline hs-TnT was undetectable in 5/11 DOX-treated women and in 2/11 TRA-treated women. By cycle 2, day +1, there was a detectable level of hs-TnT in all the DOX-treated women ($p = 0.03$) but only in 7/11 TRA-treated women ($p = ns$). Three of the four TRA-treated women with prior anthracycline exposure had the highest baseline and posttreatment hs-TnT values, while the fourth patient had no detectable level (Fig. 1). The sole patient to develop cardiac dysfunction (Table 1, patient 3) had the highest values of hs-TnT. Individual results for all patients are shown in Figure 1.

In DOX-treated women, hs-TnT increased significantly from precycle 1 to the peak of cycle 1 (4.6 ± 6.3 to 9.6 ± 12.0 pg/mL; $p < 0.03$), and from precycle 2 to the peak of cycle 2 (9.3 ± 9.2 to 16.1 ± 15 pg/mL; $p < 0.005$) (Table 3; Fig. 1). Cycle 1 baseline to cycle 2 baseline increases were significant ($p = 0.004$), as were the cycle 1 peak to the cycle 2 peak ($p = 0.002$). Day 7 posttreatment levels were not significantly different from baseline values, either for cycle 1 (6.5 ± 10.2 pg/mL) or cycle 2 (10.3 ± 9.8 pg/mL). A positive AUC of 7.1 ± 13.4 was noted for cycle 1, and the AUC increased significantly to 27 ± 19 ($p < 0.001$) in cycle 2. One woman in the DOX group developed cardiac dysfunction 3 months after the com-

Fig. 1. Individual patient data for high-sensitivity troponin T (**a, b**) and NT-proBNP (**c, d**) in women treated with doxorubicin or trastuzumab. The asterisk indicates trastuzumab-treated women with prior anthracycline exposure. Individual values of cardiac biomarkers. C1B, cycle 1, baseline; C1D1, cycle1, day 1, etc.

pletion of treatment, with a fall in EF from precycle 1 of 57 to 47%. She had the highest posttreatment value of hs-TnT (58 pg/mL) recorded during cycle 2. No significant increases in hs-TnT were seen in the TRA-treated women.

Highly significant transient increases in NT-proBNP were noted after DOX treatment, from precycle 1 to the cycle 1 peak (82 ± 50 to 363 ± 173 pg/mL; $p < 0.001$) and from precycle 2 to the cycle 2 peak (90 ± 58 to 371 ± 213 pg/mL; $p < 0.001$). AUC was positive for both cycles 1 and 2, but similar without an increase from cycle 1 to cycle 2 (427 ± 321 vs. 471 ± 323 pg/mL; ns). In the TRA-treated women, a significant increase in NT-proBNP was noted only from cycle 2 baseline to the cycle 2 peak (80 ± 71 to 206 ± 150 pg/mL; $p < 0.002$).

Discussion

In patients with myocardial infarction, cardiac troponin peaks approximately 12 h after symptom onset [8]. However, oncologic troponin research has focused on sampling distant from the administration of potentially toxic drugs, and the optimal timing for sampling is unknown. Conventional troponin assays have not yielded a reliably quantifiable early signal of troponin elevation in large percentages of patients [9, 10] and, at any rate, the assay precision is poor at low concentrations [5]. Cardinale et al. [3], using conventional troponin I (TnI) for samples early after treatment, found abnormal elevations in 65/204 (32%) of the patients receiving high-dose chemotherapy at some point, with higher percentages later in the course of treatment. All patients had normal values

at baseline, and abnormal levels were observed in 112/661 cycles. In the 65 patients who demonstrated elevated TnI, over half of the elevations were detected immediately after infusion.

Thus far, hs assays, which have improved precision at very low concentrations, have been evaluated at 3 and 6 months after treatment. Sawaya et al. [11] measured increases in ultrasensitive TnI (from 1.3 to 23 pg/mL), with the highest levels occurring at the end of therapy. Moreno et al. [12] noted increments of ultrasensitive TnI after anthracycline in 57% of patients. After cycle 3 (21-day cycles) and the completion of 8 cycles of R-CHOP including epirubicin for non-Hodgkin's lymphoma, Kang et al. [13] noted a significant increase in hs-TnT from 1 to 7.3 pg/mL.

Our data suggest that there is an early hs-TnT signal after DOX treatment, which may provide a means of quantifying myocardial damage during the initial cycles of chemotherapy in a manner that could identify patients at risk, and could allow for early pre-emptive cardioprotective medical intervention, treatment modification, or the need for posttreatment cardiac monitoring. Increases in precycle to cycle levels, in peak to peak levels, and in AUC from cycle 1 to cycle 2 suggest that myocardial damage increases with successive doses. Our pilot study was

limited by a small sample size, which prevented us from identifying a threshold value after cycles 1 or 2 which could provide confidence limit-based estimates of future risk of cardiac dysfunction. The results of similar testing in cycles 3 and 4 for DOX, and, indeed, in cycles 3–25 for TRA are unknown. Other agents given with DOX may also have influenced the results. Missing data from the kinetic analysis, requiring imputation, reduces the confidence of kinetic data.

In conclusion, cycles 1 and 2 of DOX are associated with an early rise in hs-TnT in breast cancer chemotherapy, with increases in the kinetic parameters of troponin release in cycle 2 compared to cycle 1.

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Disclosure Statement

None of the authors report a conflict of interest.

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