Dynamic Changes in High-Sensitivity Cardiac Troponin I in Response to Anthracycline-based Chemotherapy: *A pilot study for the Cardiac CARE randomised trial*

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BACKGROUND

Treatment advances have improved cancer-related outcomes and shifted interest towards minimising long-term iatrogenic complications, particularly chemotherapy-related cardiotoxicity.

High-sensitivity cardiac troponin I (hs-cTnI) assays accurately quantify very low concentrations of plasma troponin, and may enable early detection of cardiomyocyte injury prior to development of myocardial dysfunction.

The short-term kinetic profile of hs-cTnI in response to anthracycline-based treatment has not previously been described.

METHODS

- Prospective observational study
- Female patients with newly diagnosed invasive breast cancer scheduled to receive adjuvant or neo-adjuvant anthracycline-based (epirubicin) chemotherapy
- Blood sampling was performed before and 24 hours after each treatment cycle
- hs-cTnI concentrations were measured using the Abbott ARCHITECT$_{STAT}$ assay (limit of detection 1.2 ng/L, coefficient of variation ≤10% at 4.7 ng/L, 99th centile upper reference limit in women 16 ng/L, men 34 ng/L)

RESULTS

1. Between January 2016 and Aug 2017, 108 women (53.4±9.6 years; range, 31 to 77 years) were enrolled
2. The median baseline troponin concentration 1 (1 to 4) ng/L
3. When measured 24 hours following treatment, there was a median decrease in hs-cTnI concentration of 33% (p <0.001)
4. Troponin concentrations measured immediately prior to dosing increased by a median of 50% (p<0.001) with each successive treatment cycle (Figure 1)
5. 45 patients had troponin concentrations measured immediately prior to the 6th treatment cycle
6. The median (IQR) cumulative epirubicin dose was 394 (300 to 405) mg/m^2 prior to the 6th treatment cycle
7. 21 (46.6%) of patients had troponin concentrations ≥16 ng/L prior to the 6th treatment cycle indicating chronic myocardial injury
8. Troponin concentration prior to 2nd treatment cycle was a strong predictor of subsequent myocardial injury (Figure 2)

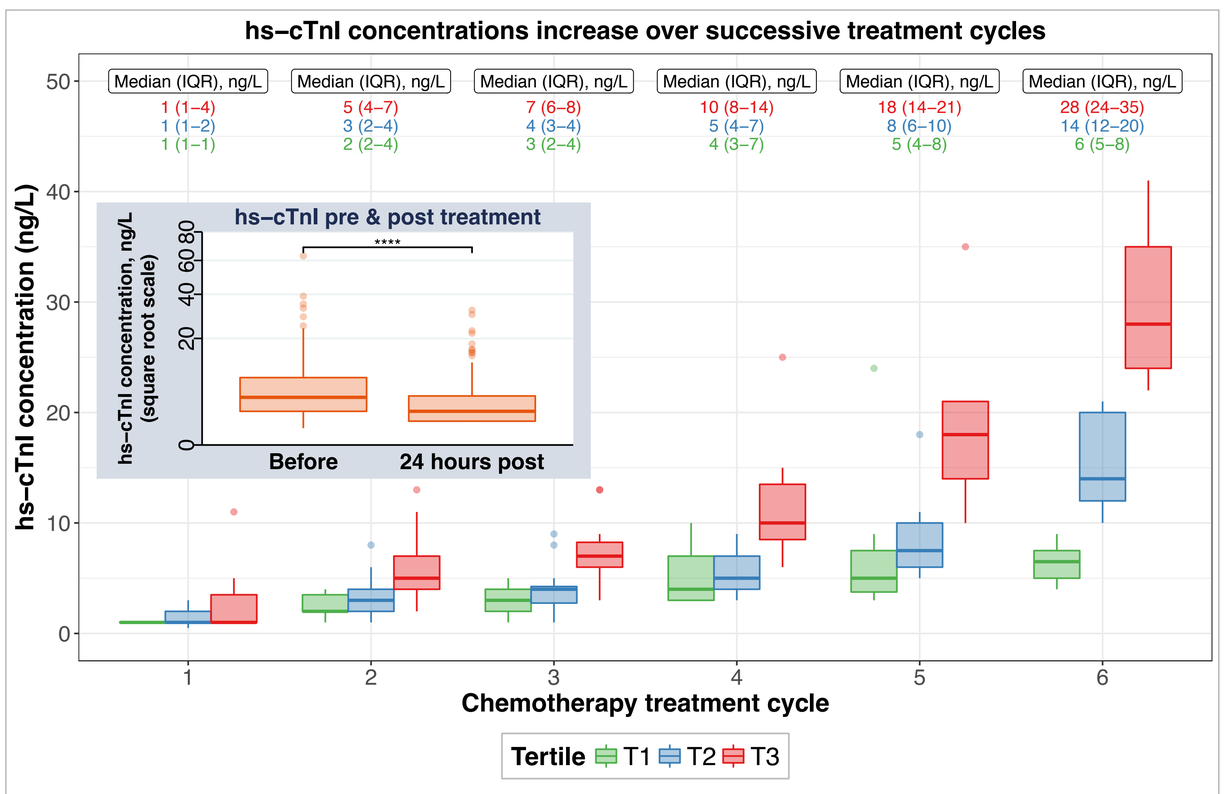

Figure 1: Median high-sensitivity cardiac troponin I concentrations immediately prior to each anthracycline dose.

Colours relate to tertiles of troponin concentration as determined prior to 6th cycle.

Inset boxplot demonstrates distribution of troponin concentrations measured before and 24 hours after each cycle.

hs-cTnI, high-sensitivity cardiac troponin I

Table 1. Baseline characteristics for total cohort and by troponin tertile*

	Total cohort	T1	T2	T3	p-value¶
n	108	15	15	15	
Age, y	53.6 (9.6)	53.1 (12.2)	53.4 (8.4)	56.1 (10.1)	0.689
BMI, kg/m^2	28.2 (5.7)	28.9 (5.5)	29.3 (6.3)	25.9 (4.4)	0.195
Hypertension	17 (15.7)	1 (6.7)	1 (6.7)	1 (6.7)	1.00
Smoking habit					0.885
Current smoker	13 (12.5)	2 (13.3)	1 (7.1)	1 (7.1)	
Ex-smoker	31 (29.8)	3 (20.0)	5 (35.7)	4 (28.6)	
Never smoked	60 (57.7)	10 (66.7)	8 (57.1)	9 (64.3)	
Diabetes mellitus	6 (5.6)	0 (0.0)	0 (0.0)	1 (6.7)	0.360
Baseline LVEF, %	63.9 (6.8)	66.1 (7.3)	63.6 (6.4)	65.5 (5.9)	0.564
Baseline hs-cTnI, ng/L	1.0 [1.0, 4.0]	1.0 [1.0, 3.0]	1.0 [1.0, 2.0]	1.0 [1.0, 4.5]	0.296†
Cumulative epirubicin dose‡, mg/m^2	394.1 [299.7, 405.4]	402.1 [398.6, 481.9]	397.2 [303.3, 404.9]	399.3 [395.2, 407.1]	0.277†

Data are mean (standard deviation), median [IQR], or value (%); BMI, body mass index; LVEF, left ventricular ejection fraction;

hs-cTnI, high-sensitivity cardiac troponin I.

*tertiles of troponin concentration as determined prior to 6th treatment cycle.

¶p-value determined from one-way ANOVA across tertile groups unless otherwise described.

†p-value determined from Kruskal-Wallis rank sum test.

‡Cumulative dose achieved prior to visit 6.

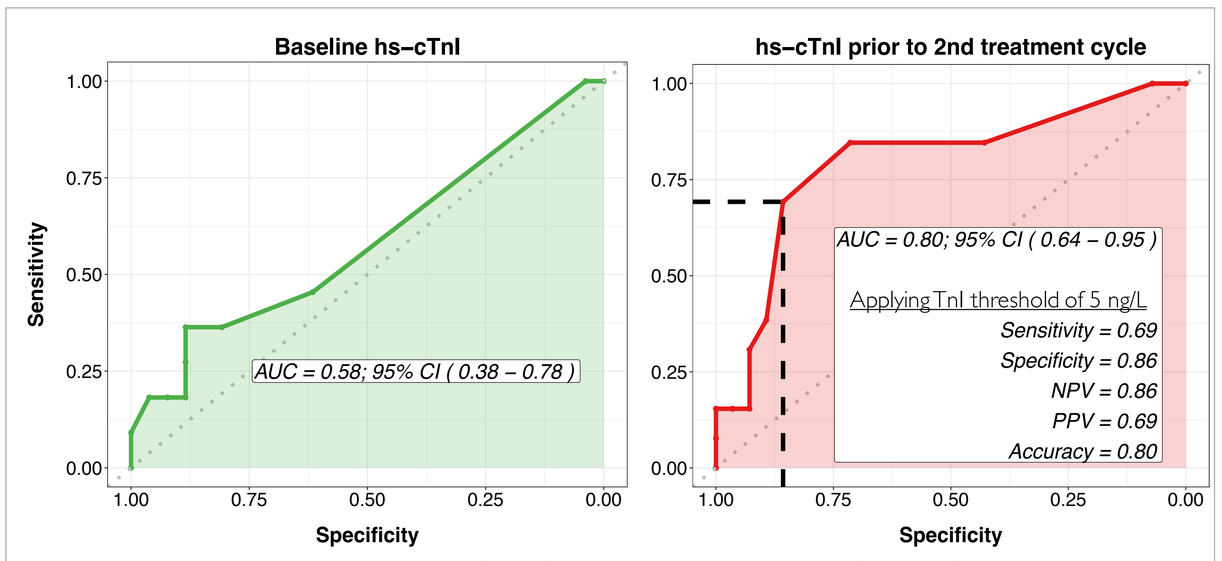

Figure 2: Receiver operating characteristic curves for the prediction of troponin concentrations in the highest tertile immediately prior to the 6th treatment cycle.

(Left) hs-cTnI concentration at baseline does not predict subsequent myocardial injury.

(Right) hs-cTnI concentration prior to 2nd treatment cycle identifies individuals at increased risk of subsequent myocardial injury with an optimal threshold of 5 ng/L.

hs-cTnI, high-sensitivity cardiac troponin I; AUC, area under curve; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value.

CONCLUSIONS

Cardiotoxicity arising from anthracycline therapy is detectable in the earliest stages of breast cancer treatment and is cumulative with each chemotherapy dose. More than a third of patients will develop biochemical evidence of chronic myocardial injury with plasma troponin concentrations above the 99th centile upper reference limit. This injury is most reliably determined from blood sampling performed before rather than after each treatment cycle.

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