

Letters to the Editor

Detection of Macrotrypsin in Patients Receiving Treatment for Breast Cancer



To the Editor:

One important variable to consider in patients with persistent elevations of high-sensitivity cardiac troponin (hs-cTn) level with unclear etiology is an interference—such as by macrotrypsin—which occur with an estimated prevalence of < 5% in hospital settings.^{1,2} Different hs-cTn assays are more apt to detect these immunoglobulin-based complexes. Although they are potentially persistent, identification of these complexes does not appear to be pathologic.²

We and others have reported previously on the high incidence of myocardial injury (ie, > 50%), as determined by hs-cTn, in women with breast cancer within the first 3 months after they started on trastuzumab following an anthracycline chemotherapy regimen.³ As these elevations in hs-cTn concentration did not correlate with a worsening left ventricular ejection fraction, our objective was to explore the possibility of the presence of a macrocomplex contributing to the observed high hs-cTn concentrations.

Plasma samples from the last 5 consecutive women who completed the study protocol (from 23 patients enrolled) were collected before chemotherapy and prior to plus-1-day post-cycles 1-9 of trastuzumab (15 samples per patient, frozen below -70°C) from our observational biomarker study (all 5 women had sufficient plasma volume to perform the analyses).³ The samples were tested with Abbott high-sensitivity cardiac troponin I (hs-cTnI; Abbott Laboratories, Abbott Park, IL) (sex-specific upper reference limit [URL] = 16 ng/L), Beckman hs-cTnI (Beckman Coulter, Brea, CA) (URL = 12 ng/L), Ortho hs-cTnI (Ortho Clinical Diagnostics, Raritan, NJ) (URL = 9 ng/L), Roche high-sensitivity cardiac troponin T (hs-cTnT; Roche Diagnostics, Basel, Switzerland) (URL = 9 ng/L), and Roche N-terminal prohormone of B-type natriuretic peptide (NT-proBNP; overall URL = 125 ng/L), with the concentrations divided by the URL to standardize interpretation. The baseline and cycle-1,-2,-9 samples were also subjected to polyethylene glycol (PEG) precipitation and tested with the Abbott hs-cTnI assay to detect the presence of macrocomplexes (macrocomplex present if PEG hs-cTnI recovery < 20%).^{2,4}

All 5 women (age range = 36-56 years) completed the same anthracycline regimen (duration range = 70-88 days) followed by 9 cycles of trastuzumab with blood collected. Before treatment (pre-chemo), only the Abbott hs-cTnI assay yielded concentrations above the limit of detection (range = 5-13 ng/L) in all samples (Supplemental Table S1), with a macrocomplex also detected with the Abbott hs-cTnI assay for

these 5 patients. The increase in hs-cTn level was similar across all assays, with the highest levels (average = 5 x URL) occurring around cycle-2 of trastuzumab (average = 96 days on treatment), which was dissimilar to the NT-proBNP profile (Fig. 1).

A larger study is necessary to determine macrotrypsin prevalence in breast cancer patients using the systematic approach recently published by the International Federation of Clinical Chemistry Committee on Clinical Applications of Cardiac Biomarkers.⁴ However, these exploratory data suggest that these macrocomplexes might explain some of the early hs-cTn elevations in this population with normal left ventricular ejection fraction.

Peter A. Kavsak, PhD
kavsakp@mcmaster.ca

Brock Hoard, BHSc
Katharine Mackett, BSc, MSc
Som D. Mukherjee, MD, MSc
Louise Bordeleau, MD, MSc
Peter M. Ellis, MD, PhD
Sukhbinder Dhesy-Thind, MD

McMaster University, Hamilton, Ontario, Canada

Ethics Statement

The study was approved by the Hamilton Integrated Research Ethics Board.

Patient Consent

Patient consent was obtained for this study.

Funding Sources

Funding sources are a Juravinski Cancer Center Foundation Grant (Dr Dhesy-Thind) and Canadian Institutes of Health Research (CIHR; Kavsak).

Disclosures

P.A.K. has received grants/reagents/consultant/advisor/honoraria from Abbott Laboratories, Abbott Point of Care, Beckman Coulter, Ortho Clinical Diagnostics, Quidel, Randox Laboratories, Roche Diagnostics, Siemens Healthcare Diagnostics, and Thermo Fisher Scientific. McMaster University has filed patents with P.A.K. listed as an inventor in the acute cardiovascular biomarker field. The other authors have no conflicts of interest to disclose.

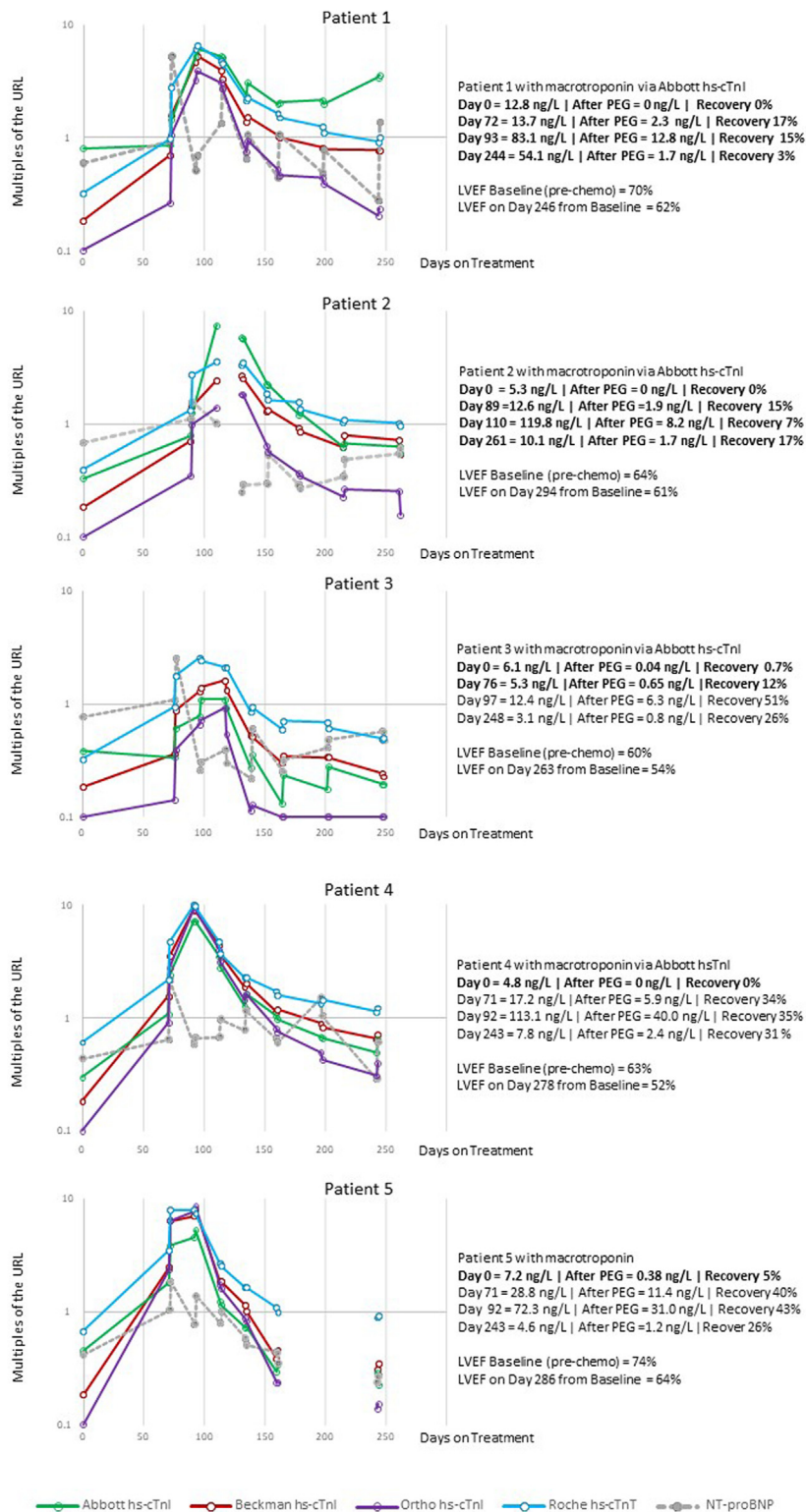


Figure 1. High-sensitivity cardiac troponin (hs-cTn) (Abbott [Abbott Park, IL], Beckman [Brea, CA], Ortho [Raritan, NJ], Roche [Basel, Switzerland]) and N-terminal prohormone of B-type natriuretic peptide (NT-proBNP; Roche) profile in 5 breast cancer patients with macrotroponin detected and left ventricular ejection fraction (LVEF) > 50% before chemotherapy (chemo) and after 6 months of treatment with trastuzumab. Macrocomplexes (bolded) detected if % recovery after polyethylene glycol (PEG) treatment is < 20% for the Abbott hs-cTnI assay. Note that for hs-cTn concentrations less than the limit of detection (< LoD), the corresponding value was substituted so the ratio to the upper reference limit (99th percentile) could be calculated: Beckman hs-cTnI = 2.2 ng/L (LoD = 2.3); Ortho hs-cTnI = 0.9 ng/L (LoD = 1); Roche = 2.9 ng/L (LoD = 3 ng/L). URL, upper reference limit.

References

1. Saunders A, Tsui AKY, Alhulaimi N. Persistent troponin elevation in the setting of an elevated rheumatoid factor: when it pays to double check. *CJC Open* 2021;3:981-3.
2. Ghossein J, Ghossein J, Booth RA, Kavsak P, Chamoun C. Presence of macrotroponin for over 2 years in a young woman. *CJC Open* 2022;4: 1012-4.
3. Dhesy-Thind S, Ellis PM, Mukherjee SD, et al. Longitudinal high-sensitivity cardiac troponin i measurements in patients with breast cancer receiving trastuzumab. *Can J Cardiol* 2019;35:545.e1-2.
4. Hammarsten O, Warner JV, Lam L, et al. Antibody-mediated interferences affecting cardiac troponin assays: recommendations from the IFCC Committee on Clinical Applications of Cardiac Biomarkers. *Clin Chem Lab Med* 2023;61:1411-9.

Supplementary Material

To access the supplementary material accompanying this article, visit *CJC Open* at <https://www.cjcopen.ca/> and at <https://doi.org/10.1016/j.cjco.2023.05.010>.