Cardiac and Inflammation Biomarker Profile after Initiation of Adjuvant Trastuzumab Therapy

To the Editor:

Liebetrau and colleagues have reported mechanistic data indicating that cardiac biomarkers appear rapidly in the blood upon induction of myocardial cell necrosis (1). Interestingly, concentrations of cardiac troponin T (cTnT) in both high-sensitivity (hs-cTnT) and fourth-generation assays continue to increase up to 1 day after the onset of necrosis. These data support the argument that irreversible myocardial injury causes prolonged release of cardiac troponin into the blood. Many anticancer therapies produce myocardial injury. Accordingly, measurement of blood cardiac biomarkers 1 day after therapy initiation may be necessary to assess whether irreversible myocardial injury has occurred. That may be important in the setting of trastuzumab treatment for human epidermal growth factor receptor 2–positive breast cancers, in which data have shown that this agent may cause cardiotoxicity, specifically a decrease in the left ventricular ejection fraction, which could lead to heart failure (2). Recent data have also suggested that inflammation (as assessed by C-reactive protein measurement) might be better than cardiac troponin I (cTnI) and the natriuretic peptides as a prognostic factor for the development of trastuzumab-mediated cardiotoxicity, although the cTnI assay used in that study was not a high-sensitivity assay (2). Moreover, earlier and additional inflammation biomarkers (as opposed to C-reactive protein) have also been demonstrated to identify the patients presenting with acute coronary syndrome (a population with a high probability of myocardial injury) who have a higher risk for subsequently developing heart failure (3). Considering these findings, we sought to determine whether changes in the concentrations of hs-cTnT (Roche assay), hs-cTnI (Abbott precommercial prototype assay), N-terminal pro-B type natriuretic peptide (NT-proBNP), heart type fatty acid–binding protein (h-FABP), and early inflammation biomarkers [e.g., interleukin-6 (IL-6), monocyte chemotactic protein 1 (MCP-1)] were evident 1 day after administering the first cycle of trastuzumab treatment.

After receiving research ethics board approval, we separated EDTA-containing plasma from whole blood collected from epidermal growth factor receptor 2–positive breast cancer patients (n = 10) as follows: at baseline (i.e., before commencing chemotherapy), on the first day before trastuzumab was administered (cycle 1/day 1), and on the next day (cycle 1/day 2). The EDTA-containing plasma samples were stored below −70 °C and thawed for the first time for the measurement of the following analytes (platforms): hs-cTnT; NT-proBNP (E module, Modular Analytics analyzer; Roche Diagnostics); h-FABP, IL-6, MCP-1 (Evidence Investigator; Randox). The samples were thawed a second time for measurement of hs-cTnI (ARCHITECT i1000SR; Abbott Laboratories) (see Table 1 for analytical precision). Statistical tests for descriptive statistics and non-parametric data were performed with Analyse-it® (Analyse-it Software) and StatsDirect software (StatsDirect); P values <0.05 were considered statistically significant.

The median age for the study patients was 57 years (interquartile range, 50–60 years). All of the patients were undergoing chemotherapy (the 10 patients received an anthracycline-containing regimen, and 5 of these patients also received paclitaxel) for a median duration of 99 days (interquartile range, 75–117 days) before they received trastuzumab. At baseline before chemotherapy, the median left ventricular ejection fraction was 57% (interquartile range, 55%–66%). The population’s concentrations for the acute cardiovascular biomarkers hs-cTnI, hs-cTnT, and h-FABP were below the reported 99th percentile cutoffs derived from a healthy population; however, comparisons with the Friedman test of analyte concentrations at baseline, at cycle 1/day 1, and at cycle 1/day 2 indicated statistically significant differences between these time points for hs-cTnI, hs-cTnT, NT-proBNP, IL-6, and MCP-1 (Table 1). Pairwise comparisons (Conover test) indicated significantly higher concentrations at day 1 than at baseline for hs-cTnI (P < 0.0001), hs-cTnT (P = 0.0003), and NT-proBNP (P = 0.025). Compared with day 1 in cycle 1, significantly higher concentrations were observed at day 2 for hs-cTnI (P = 0.0169), hs-cTnT (P = 0.0208), IL-6 (P = 0.022), and MCP-1 (P < 0.0001). For comparison, on day 2 of cycle 1, the same 6 patients had concentrations [hs-cTnI (range): 18–140 ng/L; hs-cTnT (range): 18–64 ng/L] all above the reported 99th percentiles for these assays (1, 4), as compared to 0 at baseline for both assays.

These preliminary findings indicate that there may be ongoing injury to myocardial cells that persists for at least a day after the initial trastuzumab treatment. The clinical consequences of such an

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1 Nonstandard abbreviations: cTnT, cardiac troponin T; hs-cTnT, cTnT measured with a high-sensitivity assay; cTnI, cardiac troponin I; NT-proBNP, N-terminal pro-B type natriuretic peptide; h-FABP, heart type fatty acid–binding protein; IL-6, interleukin-6; MCP-1, monocyte chemotactic protein 1.
increase are currently not known, however; we know only that, biochemically, the concentrations of hs-cTnI, hs-cTnT, and inflammation cytokines increase under these conditions. The absence of significant increases in NT-proBNP and h-FABP concentrations between day 1 and day 2 is different from the changes observed under strenuous exercise (i.e., after a marathon), in which hs-cTnT, h-FABP, and NT-proBNP are all increased at 24 h after the event (5). A larger study that assesses additional individuals at different time points after trastuzumab treatment would be needed to chart out the release kinetics of these biomarkers. Furthermore, evidence relating these biomarkers to trastuzumab-mediated heart failure is also required. Regarding the latter point, perhaps the optimal concentrations/cutoffs for cardiac troponins in high-sensitivity assays and for inflammation biomarkers could be ascertained, given that the mechanisms for release of these biomarkers after trastuzumab treatment are most likely different from other clinical settings (e.g., acute coronary syndrome) and nonclinical settings (e.g., after a marathon) in which myocardial injury is observed.

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