Biomarkers as Predictors of Cardiac Toxicity From Targeted Cancer Therapies

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ABSTRACT

Background: Cardiac biomarkers have been extensively investigated as early detectors of cardiac toxicity from cancer therapies. Whereas the role of biomarkers in monitoring anthracycline toxicity is generally well understood, substantial uncertainty remains regarding their role in monitoring newer targeted cancer therapies.

Methods and Results: This review article examines all major published studies using cardiac troponins and/or N-terminal pro–B-type natriuretic peptide (NT-proBNP) in monitoring for cardiac toxicity with trastuzumab, tyrosine kinase inhibitors, and mammalian target of rapamycin (mTOR) inhibitors. There is substantial variability among studies regarding biomarker assays used, sensitivity of the assays, and definitions of abnormal results. In general, troponin I predicts early but not late cardiac events when trastuzumab is administered after anthracyclines, but troponin increases likely reflect anthracycline injury rather than trastuzumab injury. NT-proBNP detects cardiac toxicity with tyrosine kinase inhibitors and mTOR inhibitors, but not independently from echocardiography.

Conclusions: Troponin I can serve as a marker for susceptibility to cardiac toxicity during early trastuzumab treatment in patients who have received recent anthracyclines. NT-proBNP can serve as a useful marker of cardiac toxicity in patients treated with tyrosine kinase inhibitors or mTOR inhibitors if echocardiographic screening is not being used. (*J Cardiac Fail 2016;22:459–464*)

Key Words: Cardiotoxicity, chemotherapy, trastuzumab, tyrosine kinase inhibitor.

The past 15 years have witnessed a renaissance in cancer therapeutics—with large numbers of new agents approved across a wide spectrum of malignancies. Most of these new agents have differed from traditional chemotherapy, focusing on inhibition of specific receptors or enzymes. Unfortunately, many of these agents have been associated with cardiac toxicity,[1] leading to morbidity from cardiac complications or from the cancer itself when otherwise efficacious cancer therapeutics are stopped.

Traditionally, subclinical cardiac toxicity has been detected by assessing for declines in left ventricular ejection fraction (LVEF) with the use of either echocardiography or multigated acquisition scanning. Although useful, this strategy is limited by 2 factors:

- Significant myocardial injury has typically occurred by the time declines in LVEF are apparent.
- Imaging is expensive, time consuming, and impractical to perform more than once every few months when used as a screening modality.

A potential alternate strategy for early detection of cardiac toxicity is the measurement of abnormal cardiac biomarkers in the blood. Theoretically, this strategy offers advantages over imaging as a screening tool because it is less expensive, easier to perform, and has the potential to measure toxicity at an earlier time point than imaging. This article examines the current evidence for using cardiac biomarkers as screening tools for cardiac complications of targeted cancer therapies.

Understanding the Biomarkers

Cardiac troponins are most commonly assayed in the evaluation of acute coronary syndrome, because an acute rise and fall is indicative of a myocardial infarction. However, any insult to the myocardium that results in myocardial cell death, injury,

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or increased membrane permeability can lead to elevations in circulating troponin levels.[2] Early (less sensitive) assays could only detect circulating cardiac troponins in patients with myocardial injury, leading to the assumption that it was abnormal to have detectable serum troponin levels. However, as the sensitivity of assays improved, it became clear that all individuals have measureable cardiac troponin at any given time, though typically at exceedingly low levels.[3,4] In addition, there is normal interindividual variability among normal individuals; in one study of healthy volunteers, circulating levels varied by almost an order of magnitude.[4]

Different assays can yield significantly different results, based on the specifics of the laboratory method, the degree of sensitivity of the assay, and the definition of the upper limit of normal.[3] In one study in patients receiving cancer therapy of 2 troponin assays with differing sensitivities and upper limits of normal, 9% of the samples showed discordance, with 6% of patients positive with the conventional assay and negative by the ultrasensitive assay, and 3% of patients positive with the ultrasensitive assay and negative by the conventional assay.[5]

As such, it is critical in any evaluation of a biomarker study to assess the following:

- What assay was used, and what is the lower limit of detection of the assay?
- What is the upper limit of normal defined by the manufacturer, and what have the authors chosen as the threshold for "positive" and "negative" results?
- When (in relation to cancer therapy administration) and how often were the troponin values measured? Because the half-life of troponin is only 2 hours,[2] it is possible to miss transient elevations if measured days to weeks after cancer therapy administration.

Results have been extremely disparate regarding the potential role of troponin as a biomarker to detect early cardiac toxicity of cancer therapy (Table 1). For studies of trastuzumab and using troponin I, limits of detection varied by 60-fold depending on the assay used, and the threshold of positivity defined by the studies varied by almost 3-fold.[3,6–10,12,13] In addition, troponin values are frequently reported with the use of different units of measurement, including ng/mL, ng/L, pg/mL, and μg/L. In this review, ng/mL will be used as the standard unit.

Because the primary driver for secretion of B-type natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP) is wall stress rather than myocardial injury, potential elevations in the cancer therapy population are not likely to be as specific as troponin elevations for myocardial injury. Nevertheless, dynamic changes in BNP/NT-proBNP have the potential for early detection of myocardial injury, and therefore these hormones have been investigated in the cancer therapy population.

Other biomarkers have been studied for the early detection of cardiac toxicity from cancer therapies, including galectin-3, ST-2, myeloperoxidase, and soluble fms-like tyrosine kinase receptor 1.[10,12,14–17] However, the studies have primarily focused on detection of anthracycline toxicity, and these biomarkers have not been consistently demonstrated to have a predictive role.

Table 1. Major Studies Examining the Role for Troponin Monitoring During Trastuzumab Therapy

Study	n	Troponin	Detection Threshold (ng/mL)	ULN* (ng/mL)	Positivity Threshold (ng/mL)	Cardiotoxicity Definition	Frequency of Measurements	Results
Cardinale[6]	251	I	0.03[3]	0.07[3]	0.08[6]	EF drop >10% to absolute level <50%	Every 1–3 weeks	Troponin + predicted cardiotoxicity, but + values almost exclusively at 0–2 months after anthracycline. All troponin levels normalized within 3 months even with ongoing trastuzumab.
Fallah-Rad[7]	42	T	0.005[8]	0.014[8]	0.01[7]	EF drop ≥10% to absolute level <55% necessitating trastuzumab discontinuation	Every 3 months	No troponin elevations observed
Morris[9]	95	I	0.04–0.06[9]	<0.06[3]	0.04–0.06[9]	NA (EF measured as continuous variable)	Every 2 weeks through 1st 2.5 months of trastuzumab, then every 3 months	67% had troponin +, mainly during anthracycline and first 2 months of trastuzumab treatment, then largely normalized. Degree of troponin + did not correlate with EF changes.
Sawaya[10]	81	I	0.0005[10]	0.048[11]	0.03[10]	EF drop ≥10% (or ≥5% with symptoms) to absolute level <55%	Every 3 months	Troponin + predicted cardiotoxicity only at immediate post-anthracycline time point
Ky[12]	78	I	0.014[13]	0.045[13]	NA (continuous variable)[12]	EF drop ≥10% (or ≥5% with symptoms) to absolute level <55%	Baseline and after anthracycline	Post-anthracycline troponin increases predicted cardiotoxicity, increasing risk by 40% for every 0.106 ng/mL increase

EF, ejection fraction; NA, not applicable.
*ULN, upper limit of normal, defined as 99th percentile for a healthy population.