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Utilizing Cardiac Biomarkers to Detect and Prevent Chemotherapy-induced Cardiomyopathy

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Abstract

The success achieved in advances in cancer therapy has been marred by development of cardiotoxicity, which causes significant morbidity and mortality. This has led to the development of surveillance protocols for cardiotoxicity utilizing multimodality imaging techniques and investigation of various drugs to treat and prevent cardiotoxicity in this subset of patients. Cardiac biomarkers hold important diagnostic and prognostic value in various cardiac diseases. In this review, we discuss the use of biomarkers in patients receiving chemotherapy, highlighting data behind the use of troponin, B-type natriuretic peptide and myeloperoxidase. We also discuss the use of dexrazoxane, angiotensin converting enzyme inhibitors and beta blockers in the treatment and prevention of chemotherapy induced cardiotoxicity. Cardiac biomarkers may serve as an important role in selecting patients that are at high risk of cardiotoxicity and can potentially be used to guide the administration of drugs to treat and prevent cardiotoxicity.

Keywords

Cardiac biomarkers; Chemotherapy; Cardiomyopathy; Diagnosis; Cardiac disease; B-Type natriuretic peptide

Introduction

With advances in cancer research, highly efficacious anti cancer chemotherapeutic regimens are now a reality. However this has come at a price of significant cardiotoxicity, particularly in the era of increase in the number of long term cancer survivors. The incidence of cardiotoxicity varies by the chemotherapeutic agent used but generally 5 – 20 percent for asymptomatic decrease in left ventricular ejection fraction (LVEF) to 1 to 5 percent for clinically overt heart failure (1). The cardiac side effects often limit the effectiveness of chemotherapeutics and negatively impact patient survival and quality of life. Early recognition of cardiotoxicity is therefore necessary to provide opportunities for

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individualized chemotherapy regimens and therapeutic options to prevent irreversible cardiac dysfunction.

Anthracycline chemotherapy (AC) regimens are well established and highly effective agents used to treat a variety of adult and pediatric cancers such as breast and solid organ tumors, leukemias and lymphomas. They are among the commonest chemotherapeutic agents that have been recognized to cause cardiotoxicity. The incidence of heart failure from AC is dose dependent and varies from 0.2 percent in patients receiving a cumulative dose of 3-5 percent in 400 mg/m² to 18-48 percent in patients receiving more than 700 mg/m² (2). The mechanism of cardiotoxicity is thought to be multifactorial. Among mechanisms implicated include free radical damage by reactive oxygen species leading to necrosis and apoptosis of cardiomyocytes, so called "Type I" chemotherapy related cardiac dysfunction. This may be compounded further by activation of the RAAS system (3).

Monoclonal antibodies used in cancer chemotherapy have also been implicated to cause LV dysfunction. Examples include trastuzumab, an agent that targets human epidermal growth factor receptor-2 (HER-2). These receptors are overexpressed in a subset of patients with breast cancer and serve as an important treatment target. Trastuzumab has a high incidence of cardiotoxicity, although this is usually manifested by asymptomatic LV dysfunction. Unlike AC, trastuzumab causes "Type II" chemotherapy related cardiac dysfunction where there is loss of myocyte contractility that is not usually associated with myocyte destruction. Its cardiotoxic properties are not dose dependent and may be reversible when it is discontinued (4). Rechallenge with this drug is often tolerated when myocyte recovery has been achieved. There has also been emerging data implicating Bevacizumab, a humanized monoclonal antibody against vascular endothelial growth factor, with potential cardiotoxicity, although incidence of this is low (2). Other chemotherapeutic agents that have been implicated to cause cardiotoxicity include sunitinib, sorafenib and lapatinib, members of group of tyrosine kinase inhibitors on vascular endothelial growth factor (VEGF) receptors and HER-2 receptors respectively.

Current recommendations for monitoring of functional capacity of the heart in chemotherapy patients is performed by evaluating the left ventricular ejection fraction (LVEF) either by transthoracic echocardiography or radionuclide ventriculography, with specific timepoints depending on type of chemotherapy used, presence of risk factors as well as dose used (5). Transthoracic echocardiography has become the preferred option owing to its lack of radiation and ability to provide a variety of other information including diastolic and valvular function. When available, the use of strain and three dimensional imaging has been used to monitor for cardiotoxicity. However, this resource can be costly, particularly in patients with intense monitoring due to repeated scans, and its accuracy and reproducibility highly operator dependent. In this review, we explore the role of cardiac biomarkers in the field of cardio-oncology.

Troponin

The utility of troponin as an early marker of cardiac injury has been increasingly recognized. Troponin is a protein found in the contractile machinery of the cardiac myocytes and has 3

subunits: T, I and C. The cardiospecific isoenzymes of troponin I (cTnI) and troponin T (cTnT) are released into the blood when cardiac myocytes are damaged due to a wide variety of clinical conditions including acute coronary syndromes, heart failure, pulmonary embolism and from direct toxic effects of drugs (6-10).

Its role in the detection of chemotherapy induced cardiotoxicity has been demonstrated in multiple studies. Herman et al., demonstrated that in spontaneously hypertensive rats, serum cTnT levels correlated with cumulative doxorubicin dose and the severity of cardiac injury (11). Similar results were seen in daunorubicin treated rabbits and doxorubicin treated rats (12, 13). These studies found that increasing cTnT levels were correlated with worsening left ventricular contractility, and rise in cTnT levels were antecedent to deterioration of cardiac function demonstrating the diagnostic and predictive value of troponin measurement. The use of troponin has also been extensively studied in pediatric and adult populations. Cardinale et al., demonstrated in multiple studies the efficacy of early cTnI measurements in predicting future LVEF depression in patients undergoing high dose chemotherapy (HDC) (14-17). In two other series of 211 and 179 HDC patients respectively, cTnI positivity was found to be predictive of greater decrease in LVEF at one month follow up (16, 17).

In addition to portending risk of cardiomyopathy, cTnI measurement has also been shown to be clinically useful in cardiovascular risk stratification. In a study of 703 patients undergoing HDC, cTnI was measured at an early evaluation (during 3 days following each HDC cycle) and late evaluation (one month after last HDC) with patients being classified into three groups: cTnI $+/+$ (9%), cTnI $+/-$ (21%) and cTnI $-/-$ (70%) (18). Over a 3.5 year follow up period, the rates of adverse cardiac events in the three groups were 84%, 37% and 1% respectively. Importantly, no signs of LVEF decrease were observed in the cTnI $-/-$ group.

Studies have demonstrated a strong association between cTnT positivity and echocardiographic abnormalities. Auner et. al., studied 78 patients receiving AC for hematological malignancies and reported a greater decrease in LVEF in cTnT+ patients compared to cTnT- patients (10% vs 2%, $p=0.017$) (19). In a study of 75 patients with receiving AC for non-Hodgkins lymphoma, both a rise in cTnT and decrease in global longitudinal strain imaging measured between baseline and third cycle of chemotherapy predicted subsequent development of cardiotoxicity later in life (20). Sawaya et al., first found that in 43 patients receiving AC and trastuzumab for breast cancer, a decrease in longitudinal strain together with a detectable level of ultra sensitive troponin I at 3 months subsequently predicted cardiotoxicity at 6 months (21). As illustrated in Figure 1, patients who developed cardiotoxicity had greater decrease in longitudinal strain. When combined with ultrasensitive TnI positivity, a decrease of more than 10 percent of longitudinal strain had a 95 percent specificity for development of cardiotoxicity. In this cohort, parameters of diastolic dysfunction as well as N-terminal pro BNP did not predict cardiotoxicity. These findings were again replicated in 81 women with breast cancer treated with trastuzumab, taxanes and AC, both systolic longitudinal strain and ultrasensitive cTnI predicted subsequent cardiotoxicity (22). In a group of 41 patients receiving AC, increases in cTnT was found to correlate with parameters of diastolic dysfunction (23).

There is established literature regarding the use of dexzorozone, ACE inhibitors and beta blockers to be beneficial in treating or preventing chemotherapy induced cardiomyopathy (24-26). In 50 patients with ALL receiving AC cardiotoxicity, El-Shitany et. al., demonstrated that the group of patients randomized to receive carvedilol with had less LV dysfunction and less troponin and LDH release compared to the group receiving AC alone (24).

Experimental models also suggest there is activation of the renin-angiotensin system in addition to increased oxidative stress as a possible mechanism in development of chemotherapy induced cardiotoxicity. In an exploration of biomarkers in patients receiving trastuzumab chemotherapy, NT-pro BNP levels were found to be elevated despite normal troponin levels in patients with LVEF receiving trastuzumab, suggesting the role of subclinical cardiac strain and possible activation of the RAS system (27). The role of angiotensin converting enzyme (ACE) inhibitors/Angiotensin receptor blockers (ARBs) in preventing cardiac dysfunction following chemotherapy has been investigated in multiple studies, and troponin may be a useful biomarker in identifying a high risk patients that are candidates for treatment for cardiotoxicity. In a group of 473 patients receiving HDC, Cardinale et. al., randomized 114 patients with elevated TnI to receive enalapril vs. no treatment 1 month after completion of chemotherapy for 1 year with primary end point of an absolute decrease >10% in LVEF (28). The group receiving enalapril has significantly lower incidence of the primary endpoint (0% vs. 43%) and lower incidence of adverse cardiac events (2% vs. 52%). Studies with ARBs telmisartan and valsartan have also demonstrated similar cardioprotective effects in patients undergoing chemotherapy (29, 30) as well as the utility of ACE inhibitors in reversing LVEF decrease (31).

Combination therapy with ACE inhibitors and beta blockers has also been investigated with multiple studies showing significant beneficial effects of combination therapy (32, 33). In a series of 201 patients with LVEF <45% due to anthracycline induced CM, cTnI was measured before, immediately after and at 12, 24, 36 and 72 hours after every cycle of HDC with echocardiograms obtained before HDC, monthly for 3 months and 3 monthly for the first two years (15). Most cTnI positivity occurred soon after the end of drug administration and there was evidence of LVEF reduction from three months onwards. The cTnI+ patients had a significant reduction in LVEF (<50%) as compared to cTnI- group (29% vs 0%) and the maximal cTnI value strongly correlated with maximal LVEF reduction. In this group, enalapril was first initiated at 2.5-5mg/day and in patients receiving at least 5mg/d of enalapril, carvedilol 6.25mg/day was added. The mean follow up for the study was 36 months. Forty-two percent of the patients had a LVEF recovery to normal values of 50% and 13% had at least a 10 point increase in LVEF. The responders were more likely than non-responders to have tolerated a combination of enalapril and carvedilol and had a significantly shorter time to HF treatment. In patients where the treatment was started within 2 months of completion of chemotherapy, 64% of patients achieved complete LVEF recovery. However, if HF treatment was more than 6 months after completion of chemotherapy, none of the patients had complete LVEF recovery. The study was important not only demonstrating benefits of combination therapy, but also illustrated the impact of time to initiation of HF therapy in the treatment of this disease.

Measurement of troponin has also been used to predict reversibility of cardiotoxicity in patients receiving trastuzumab. In a large series of 251 patients receiving trastuzumab, there was a higher incidence of cardiotoxicity in cTnI + patients compared to cTnI- patients (62% vs 5%). Sixty percent of these patients had LVEF recovery after stopping trastuzumab and initiating HF therapy with carvedilol and enalapril. In this study, cTnI+ predicted the development of cardiotoxicity and non-recovery of LVEF. In two other studies of 95 and 43 breast cancer patients receiving trastuzumab, cTnI elevation was found to precede cardiac dysfunction and predictive of future cardiac dysfunction (21, 34).

Dexrazoxane is an iron chelating agent (35) that has been shown to be cardioprotective in patients undergoing anthracycline based chemotherapy (36-39). Patients receiving dexrazoxane with doxorubicin for ALL (ten doses of 30 mg/m²) was less likely to have troponin elevation compared to those not receiving this drug (21% vs. 50%) (38). This group also had better left ventricular fractional shortening and end-systolic dimension Z scores, significantly fewer cardiac events (27.7% vs 52.4%) and less severe CHF (6.4% vs 14.3%) at a 5 yr follow up when compared to patients receiving AC alone.

While there is a large body of data demonstrating the predictive value of troponin measurements, there are studies that have failed to show such predictive utility. Dodos et al., studied 100 patients receiving anthracycline therapy and measured cTnT before, 3-5 days after first dose and at 3 days, 1, 6 and 12 months after the last course of chemotherapy (40). They found that cTnT elevations were not predictive of a concomitant decrease in LVEF. In two other series of 29 and 31 patients undergoing anthracycline therapy for heme malignancies, cTnI was measured once, one month after the end of chemotherapy. It showed no elevation and no correlation with cardiac dysfunction (41, 42). Kismet el al., measured TnT in 24 patients who had previously received anthracycline therapy (43). The median length of time from last chemotherapy dose was 12 months. They did not find any correlation between TnT levels and cardiac function. Koseoglu et al., conducted a study with 22 patients who had received doxorubicin. 64% of the patients had completed therapy in the past with a median time of 31 months from the last dose, the other 36% of patients were still on treatment (44). Only one sample of TnI and one time echo study was conducted for each patient. They found cardiac dysfunction in 3 patients but no TnI elevations in any patient. They found no correlation between TnI and echo parameters. Fallah-Rad et al., prospectively followed 42 patients receiving trastuzumab (45). cTnT was measured at 6 time points, before anthracycline therapy, before trastuzumab therapy (3 weeks after final cycle of chemotherapy), 3, 6, 9 and 12 months after initiation of trastuzumab. They found no difference in cTnT values between patients who developed cardiotoxicity compared to patients who did not develop cardiotoxicity.

Studies that show positive predictive value of troponin measurement are usually of larger case series, with more intensive troponin measurements and longer echocardiographic follow ups (Table 1). Most of the troponin elevations were reported immediately after chemotherapy, and the rest of the positive values were homogeneously distributed along the entire follow up time course (Table 2). This suggests troponin elevation is time sensitive and there is risk of missing an elevation if close monitoring is not performed. In some of the studies that failed to show a predictive value of troponin, troponin was measured weeks to

months after the final dose of chemotherapy, and there were fewer measurement points and smaller sample size. This highlights the need to have systematic and intensive troponin monitoring during the entire course of chemotherapy as it can provide foresight to potentially life threatening cardiac dysfunction in the future. Incorporating information from all the studies, a proposed sampling protocol could include: troponin measurements at baseline, then immediately after, at 1, 2 and 4 days after drug infusion for each chemotherapy cycle, then 1 week, 1 month and 2 months after the last cycle.

Brain natriuretic peptides

Brain natriuretic peptides (BNP) are synthesized and released by left ventricular cardiomyocytes secondary to wall stress and serve to promote natriuresis, diuresis, vasodilation and suppression of sympathetic activation (46). Upon synthesis, it is cleaved to pro BNP before undergoing further cleavage to N-Terminal pro BNP (NT-pro BNP) and active hormone BNP. This family of biomarkers have well established clinical utility, including diagnostic and prognostic value in heart failure (47, 48).

Numerous studies have investigated trends in BNP and NT-pro BNP levels in patients receiving chemotherapy, including AC based and trastuzumab chemotherapy with mixed results. When measured just before and 24 hours after receiving non-high dose anthracycline chemotherapy in patients with breast cancer, persistent elevation in NT-pro BNP levels were found to be predictive of LV impairment in 3, 6 and 12 months of follow up (49). Significant elevations in NT-pro BNP levels were also seen in patients with breast cancer receiving epirubicin based chemotherapy, and this correlated with decline in ejection fraction and development of clinical heart failure (50).

Data with BNP levels in patients receiving trastuzumab therapy is less clear. Higher pre-treatment NT-pro BNP levels were seen in 17 patients receiving trastuzumab chemotherapy who subsequently developed heart failure (51). However in 42 patients with human epidermal growth factor receptor II-positive breast cancer patients treated with trastuzumab, measurements of troponin, CRP and NT-pro BNP did not hold any predictive value in the 10 patients that subsequently developed cardiomyopathy (45). NT-pro BNP was also not found to be significantly predictive for cardiotoxicity in two other cohorts of breast cancer patients receiving neoadjuvant trastuzumab therapy (21, 52).

Like troponin, BNP has also been shown to decrease in patients receiving preventative treatment for chemotherapy induced cardiomyopathy. In pediatric patients with ALL receiving doxorubicin, patients randomized to receive concurrent dexrazoxane had fewer BNP elevations post treatment with doxorubicin (20% vs. 48%) (53).

Myeloperoxidase

Myeloperoxidase (MPO) is an enzyme that is involved in lipid peroxidation and released in periods of proinflammatory oxidative stress by polymorphonuclear neutrophils. In contrast to C-reactive protein, growth differentiation factor, placental growth factor, galactin -3 and soluble fms-like tyrosine kinase receptor, increases of MPO and troponin I when measured 3 months was found to be a predictor of cardiotoxicity in patients with breast cancer receiving

anthracyclines, taxanes and trastuzumab (52). More importantly, the measurement of MPO, when combined with cTnI, provided incremental sensitivity and specificity in predicting cardiotoxicity.

Summary

In this review, we discussed the role of biomarkers in the evaluation of chemotherapy induced cardiomyopathy, highlighting some of the pivotal studies and data published to date. Biomarkers such as troponin, MPO and BNP, either in isolation or when used together may provide incremental information in highlighting a high risk group of patients who are at risk of significant cardiotoxicity and poor outcomes. Early recognition of cardiotoxicity with elevated biomarkers through intensive sampling protocol is critical to provide the best chance of LVEF recovery and we therefore propose aggressive biomarker monitoring in patients chemotherapy. Dexrazoxane therapy should be considered in patients receiving AC above 300 mg/m². In most cases of cardiomyopathy, combination therapy with ACE inhibitors and blockers appear to be synergistic and more efficacious than either of these agents alone and may have a role in long term management of these patients. Indeed, biomarkers of cardiac injury may provide cheaper, quicker, easier, more reproducible and possibly superior monitoring means into the development of cardiotoxicity.

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Figure 1. Individual changes in the LVEF (A) and longitudinal strain (B) in patients who did not develop (left) and those who developed (right) cardiotoxicity (21). *Permission obtained.*

Table 1
Time of troponin measurements in studies that show a predictive value of troponin measurements

Study	Population studied	n	Troponin type	Time course of troponin measurement	Conclusions
Cardinale et al., 2000 (14)	High dose chemotherapy for aggressive malignancies	204	I	Baseline, then 0, 12, 24, 36 and 72 h after every single cycle of chemotherapy.	cTnI elevation accurately predicts the development of future LVEF depression
Auner et al., (19)	Heme malignancies/142 cycles including anthracyclines	78	T	Baseline, first 48 hr after initiation of chemotherapy, then every 48 hr afterwards until discharge. This process repeated for every chemotherapy cycle.	Serial cTnT identifies subclinical myocardial damage and identifies patients at risk of subsequent dysfunction.
Cardinale et al., 2002(16)	Patients receiving high dose chemotherapy for high risk breast cancer.	211	I	Baseline, 0, 12hr, 24hr, 36hr and 72 hr after each cycle of HDC.	cTnI elevation soon after HDC accurately predicts the development of future LVEF depression.
Sandri et al., 2003 (17)	High dose chemotherapy for aggressive malignancies.	179	I	Baseline, 0, 12hr, 24hr, 36hr and 72 hr after each cycle of HDC	cTnI detected detect minor myocardial injury as evidenced by drop in LVEF in patients treated with high dose chemotherapy.
Cardinale et al., 2004 (18)	High dose chemotherapy for advanced or resistant breast cancer	703	I	Baseline, 0, 12hr, 24hr, 36hr and 72 hr after each cycle of HDC.	cTnI rise identifies patients with high risk of cardiac events >/3 years
Cardinale et al. 2010(15)	Adjuvant trastuzumab therapy for breast CA	251	I	Baseline, immediately after each chemotherapy cycle, at each cardiologic check after completion of the therapy	cTnI predicted patients with high risk of cardiac events and this risk was modified by early aggressive medical treatment.
Killickap et al., 2005 (23)	Solid or hematologic malignancy. Receiving anthracycline containing CT.	41	T	Baseline, 3-5 days after 1st cycle, after last cycle	cTnT levels detected in the early stages of AC is associated with diastolic dysfunction.
Morris et al., 2011 (34)	Breast cancer patients treated with dense chemotherapy incorporating trastuzumab and lapatinib	95	I	Baseline, every 2 weeks during chemotherapy, then at 6, 6 and 18 months	cTnIs elevations may precede changes in LVEF but did not predict CHF
Sawaya et al., 2011 (21)	Breast cancer patients treated with anthracyclines and trastuzumab	43	I	Baseline, then at 3 and 6 months during the course of chemotherapy	cTnI and longitudinal strain predict cardiotoxicity in patients treated with AC and trastuzumab.

Table 2
Time of troponin elevation

Study	Time of TnI increase
Cardinale et al., 2000 (14)	In 53% soon after the end of drug admin, In 9% after 12h In 19% after 24h In 7% after 36h In 12% after 72hr In TnI +, LVEF sig dec from 3 months onwards In TnI-, LVEF dec after 3 months but recovered to baseline at 4-7 months
Cardinale et al., 2002 (16)	30% right after 27% at 12hr 25% at 24hr 10% at 36hr 13% at 72hr LVEF dec in TnI+ at 1 month
Sandri et al., 2003 (17)	+ results were homogenously distributed along the 6 time points of TnI curve.
Cardinale et al., 2004 (18)	33% soon after 22% after 12 hr 8% after 24hr 24% after 36hr 13% after 72hr
Cardinale et al. 2010 (15)	Most TnI positivity right after the first trastuzumab cycle
Auner et al., 2003 (19)	Tnt+ seen day 4-day 35. peak seen day 21.5
Killickap, 2005 (23)	2 had inc. after first cycle (3-5d after Tx) 14 had elevation after therapy
Sawaya et al., 2011 (21)	67% had elevations at 3 month measurement 33% had elevation at 6 month measurement