Chapter 24
Biomarkers in Specific Disease States: Cardio-Oncology

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Abstract Cancer related mortality has been dramatically reduced in recent decades due to more effective cancer treatments, especially chemotherapy and radiation therapy. However, the use of these treatment modalities may be limited by the risk of significant cardiac damage. The current standard for cardiac safety assessment, in order to limit cardiotoxicity, predominantly focuses on serial cardiac imaging to identify changes in left ventricular ejection fraction (LVEF). Unfortunately, this method is imperfect and frequently is a late finding. Potentially permanent cardiac damage manifesting as a significantly reduced LVEF has to occur before any important change in management is undertaken. One alternative and complimentary approach is the appropriate use of cardiac biomarkers to identify subclinical cardiac damage allowing for earlier detection and institution of cardio-protective interventions. This chapter will highlight the clinical use of cardiac biomarkers, specifically natriuretic peptides, cardiac troponins, as well as emerging biomarkers, for the detection of cardiac injury in the context of cardio-oncology.

Keywords Biomarker • Cardio-Oncology • Heart failure • Cardiac toxicity • Anthracyclines • Troponin • Natriuretic peptides

Cancer and cardiovascular diseases are by far the most common diseases resulting in mortality in the developed world [1]. The last decade has seen a profound increase cancer therapeutic options and the efficacy of those treatments [2]. Consequently, there is an ever increasing cohort of patients who are long-term survivors of childhood and adult onset cancer [3]. As this patient population ages, there is an increasing overlap with concomitant cardiovascular disease (CVD) [4–6]. It appears that CVD in survivors may be an epidemiological consequence of aging but also is

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related to the toxicity of chemotherapy, radiation therapy or other treatments for cancer [6, 7]. Furthermore, a substantial portion of cancer patients may have pre-existing CVD which can be unmasked or exacerbated by increasingly specific chemotherapeutic agents with cardiotoxic effects. Cardiac damage may occur in a myriad of ways including arrhythmias, myocardial ischemia, hypertension, left ventricular (LV) dysfunction and heart failure (HF) [8–11]. Additionally, there are a host of vascular complications that may arise during and after treatment [12]. Encouragingly, there is also evidence that early detection of cardiovascular damage with initiation of cardiovascular based medical therapy can prevent and/or enhance cardiac recovery in the case of LV dysfunction but also prevention of toxicity with control of vascular complications [13–16]. The main limitation is related to detecting cardiovascular dysfunction at an early stage and initiating therapy before permanent damage occurs. The emphasis, thus, has been on cardiac imaging modalities including echocardiography with and without LV deformation (strain), multiple gated acquisition scan (MUGA) and cardiac magnetic resonance imaging (cMRI) to hopefully detect damage at an early point [17–21]. Unfortunately, the detection of a significant change in LVEF by any of these modalities is generally a late finding and usually indicates substantial underlying cardiac damage and remodeling [6, 22, 23]. The challenge at the present time is to be able to identify cardiac damage at the earliest stage prior to a reduction in LVEF and initiate therapy or modify dosing to prevent LV dysfunction. One way of achieving this goal is to utilize cardiac biomarkers to identify those at risk for developing cardiotoxicity. Overall, the advantage of cardiac biomarkers is that it is generally much less expensive, can be followed with ease in a serial fashion, and are less subject to interpretative variation [22]. In this chapter we will examine the data supporting the use of cardiac based biomarkers to enhance safety and cardio-protection during therapy for cancer.

B-type Natriuretic Peptide

B-type natriuretic peptide (BNP) is a neurohormone polypeptide secreted by the myocytes of the ventricles in response to increased wall stress from volume expansion and pressure overload and is secreted along with a 76-amino acid N-terminal pro BNP (NT-proBNP), that is biologically inactive, and eventually cleaved to the active 32 amino acid BNP [24]. The hemodynamic effects of BNP include a decrease in afterload and increase in natriuresis; thus, counteracting some of the pathophysiologic mechanisms responsible for the progression of HF. Robust data from the Breathing Not Properly trial (BNP trial) demonstrated that BNP was able to differentiate congestive heart failure (CHF) from non-CHF causes of dyspnea with good specificity and high negative predictive values. Subsequent studies also showed the utility of BNP for prognosis and risk stratification in the setting of HF [25, 26]. Additionally, NT-proBNP–guided optimal medical therapy is associated with a reduced incidence of cardiovascular death, new episodes of decompensated HF, and

reduction in NT-proBNP that also correlates with LV remodeling and recovery [27]. Based on the aforementioned clinical utility, it comes as no surprise that the natriuretic peptides, BNP/NT-proBNP, can be useful in the setting of early detection of potential cardiotoxicity due to its ability to detect subclinical disease, direct medical therapy and assist with prognostication even prior to a decline in LVEF [28, 29].

Multiple studies have looked at the utility of perturbations in BNP/NT-proBNP levels in patients with cancer undergoing treatment with chemotherapy or radiation (Table 24.1). In one such study, patients receiving high dose anthracyclines for breast cancer, NT-proBNP was measured at baseline and immediately following each treatment cycle [30]. There was a high degree of correlation between a rise in NT-ProBNP and a reduction in LVEF. Similar findings with natriuretic peptides were replicated in other studies primarily with the use of anthracycline-based chemotherapeutic regimens [28, 29]. The utility of BNP to assist in identifying those patients at risk for cardiotoxicity and LV dysfunction goes beyond the acute setting. Persistently elevated BNP is predictive of late onset adriamycin-induced cardiotoxicity and correlates with cardiac dysfunction detected over time [6, 28–30]. Furthermore, a baseline elevation of BNP can mark a patient at high risk for the development of cardiotoxicity during subsequent rounds of chemotherapy [16].

Aside from predicting subsequent cardiotoxicity predominantly with anthracycline-based treatment, natriuretic peptide (NP) levels may indicate a potential therapeutic benefit. In one study, children with acute lymphoid leukemia (ALL) were randomized to receive doxorubicin with or without dexrazoxane (a cardioprotective free radical scavenger) and those patients given dexrazoxane tended to have reduced NT-proBNP concentrations indicating a cardioprotective effect (47 vs. 20 %, $p = 0.07$) [31]. It is especially important to have cardioprotective strategies in the pediatric population that have increased long-term survival into adulthood [5, 32]. Additionally, NT-proBNP levels were lower and the LV mass was reduced in a pediatric patient population nearly 4 years after anthracycline treatment (p =0.003) [32]. Consequently, NT-BNP/BNP levels appear to guide providers in identifying those specific patients at risk for toxicity as well as indicating what therapeutic interventions may reduce the impact of cardiac dysfunction with anthracyclines.

The utility of natriuretic peptides (NP) to assist in detecting cardiac damage during cancer therapy can extend to a broader population than just those receiving known substantial cardio-toxins like anthracyclines. For instance, those patients receiving chest radiation, those at risk for development of atrial fibrillation while receiving anti-VEGF based therapy, those at risk for HF with tyrosine kinase inhibitors, and potentially those receiving combination therapy for multiple myeloma all may be populations in which NP may be useful [16, 33–35]. Elevated BNP levels correlate with an increased risk for radiation induced cardiomyopathy (early and late) and are directly related to the amount of radiation delivered [33]. Furthermore, NT-proBNP levels are used to stage and predict outcomes in patients with AL amyloidosis as well as monitor response to therapy [36–38].

Table 24.1 Role of natriuretic peptides in the evaluation of chemotherapy and radiation-induced cardiotoxicity*

Reference	Population	N	Treatment	BNP type	Cutoff	BNP evaluations	Results and conclusions
Meinardi et al.	Breast cancer	39	ACs and RT	BNP	10 pmol/l	Baseline, 1 month, and 1 year after chemotherapy	BNP increased as early as 1 month after chemo; no correlation with LVEF decline
Nousiainen et al.	Non-Hodgkin lymphoma	28	CHOP	BNP	227 pmol/l	Baseline, after every cycle, and 4 weeks after last cycle	Correlation between BNP increases and parameters of diastolic function (FS and PFR)
Daugaard et al.	Various	107	ACs	BNP		Before, and at various points during treatment	BNP correlation with decreased LVEF, but baseline and BNP change could not predict LVEF decline
Perik et al.	Breast cancer	54	ACs and RT	NT-proBNP	10 pmol/l	Median 2.7 and 6.5 years after chemotherapy	BNP increased with time and was related to dose; cardiotoxic effects develop over years
Sandri et al.	Various	52	HDC	NT-proBNP	153 ng/I (M <50), 227 ng/l (M >50), 88 ng/l (F <50), 334 ng/l (F >50)	Baseline, and 0, 12, 24, 36, and 72 h after each cycle	Persistent NT-proBNP elevation at 72 h predicts later systolic and diastolic dysfunction
Germanakis et al.	Pediatric cancers	19	ACs	NT-proBNP	0.2 pmol/ml	Mean 3.9 years after chemotherapy	Correlation between NT-proBNP and LV mass decrease
Perik et al.	Breast cancer	17	ACs and T	NT-proBNP	125 ng/I	Baseline and throughout T treatment	H igher pre-treatment NT-proBNP values in those who developed HF during treatment

Aggarwal et al.	Pediatric cancers	63	ACs	BNP		Once, >1 year after treatment completion	Higher BNP in patients with late cardiac dysfunction by ECHO
Ekstein et al.	Pediatric cancers	23	ACs	NT-proBNP	350 pg/ml	Before and after each AC dose	Dose-related increase in BNP from baseline seen after first AC dose
Jingu et al.	Esophageal cancer	197	RT	BNP		Before, <1 month, 1–2, 3–8, 9–24, and >24 months after RT	Increased BNP over time and in those with abnormal FDG accumulation
Kouloubinis et al.	Breast cancer	40	ACs	NT-proBNP		Before and after chemotherapy	Correlation between NT-proBNP increase and LVEF decline
Dodos et al.	Various	100	ACs	NT-proBNP	153 or 227 ng/l for M <50 or >50; 88 or 334 ng/l for F <50 or >50	After first dose, last dose, and 1, 6, and 12 months after last dose	No significant increase in NT-proBNP with treatment; cannot replace serial ECHO for monitoring of AC-induced cardiotoxicity
Kozak et al.	Lung and esophageal CA	30	ChemoRT	NT-proBNP		Baseline, after 2 weeks of RT, and after RT end	No change in NT-proBNP during treatment
Cil et al.	Breast cancer	33	ACs	NT-proBNP	110 pg/ml	Before and after chemotherapy	Despite association, pre-chemo NT-proBNP did not predict for later LVEF
ElGhandour et al.	Non-Hodgkin lymphoma	40	CHOP	BNP		Before first cycle and after sixth cycle of chemotherapy	Correlation between BNP values after chemotherapy and LVEF

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Table 24.1 (continued)

Reference	Population	N	Treatment	BNP type	Cutoff	BNP evaluations	Results and conclusions
Mavinkurve-Groothuis et al.	Pediatric cancers	122	ACs	NTproBNP	10 pmol/l (M), 18 pmol/l (F), age-adjusted in children	Once, with imaging	NT-proBNP levels related to cumulative AC dose
Nellessen et al.	Lung and breast CA	23	RT	NT-proBNP	100 pg/ml	Before RT, every week during RT for 4–6 weeks	Log-transformed NT-proBNP increased during treatment
Fallah-Rad et al.	Breast cancer	42	ACs and T	NT-proBNP		Before chemotherapy, before T, and 3, 6, 9, and 12 months after start of T	No change in NT-proBNP values over time
Feola et al.	Breast cancer	53	ACs	NT-proBNP	5 pg/ml	Baseline, after 1 month, 1 and 2 years	NT-proBNP increased acutely with treatment, and in patients with systolic dysfunction
Goel et al.	Breast cancer	36	ACs and T	NT-proBNP	110 pg/mI (age <75), 589 pg/mI (age >75)	Baseline, before and 24 h after T	No change in NT-proBNP with trastuzumab
Romano et al.	Breast cancer	92	ACs	NT-proBNP	153 pg/ml (age <50), 222 pg/ml (age >50)	Every 2 weeks during treatment, then at 3, 6, and 12 months	Interval change in NT-proBNP predicated for LV impairment at 3, 6, and 12 months
Sawaya et al.	Breast cancer	43	ACs and T	NT-proBNP	125 pg/ml	Baseline, 3 and 6 months after chemotherapy	No relation between NT-proBNP levels before and after treatment and LVEF change
D'Errico et al.	Breast cancer	60	ChemoRT	NT-proBNP	125 pg/ml	Before and after RT	Correlation between NT-proBNR V3G_y for the heart, D15$_{crn}$2/Dmean and D$_{15cm}$3/D50%

Lipshultz et al.	ALL	156	ACs	NT-proBNP	150 pg/ml (age <1), 100 pg/ml (age >1)	Before, and daily during induction, and after treatment	Correlation between NT-proBNP and change in LV thickness-to-dimension ratio 4 years later
Mladosievicova et al.	Childhood leukemias	69	ACs	NT-proBNP	105 pg/ml (F), 75 pg/ml (M)	Median 11 years after treatment	Increased NT-proBNP with exposure to ACs
Onitilo et al.	Breast cancer	54	Taxanes and T	BNP	200 pg/ml	Baseline and every 3 weeks during treatment	No correlation between elevated BNP values and cardiotoxicity
Prongprot et al.	pediatric cancers	30	ACs	NT-proBNP	Age-adjusted (100)	Once, with imaging	Correlation between NT-proBNP values and FS and LVEF
Sawaya et al.	Breast cancer	81	ACs and T	NT-proBNP	125 pg/ml	Before, every 3 months during and after T treatment	NT-proBNP did not change with treatment
Sherief et al.	Acute leukemias	50	ACs	NT-proBNP	Age-adjusted (107)	Once, with imaging	NT-proBNP linked to AC dose and abnormal tissue Doppler imaging parameters
Kittiwarawut et al.	Breast cancer	52	ACs	NT-proBNP	45 pg/ml	Baseline and end of fourth cycle	Correlation between NT-proBNP and FS
Ky et al.	Breast cancer	78	ACs and T	NT-proBNP		Baseline, 3 and 6 months after start of chemotherapy	No relationship between NT-proBNP values and cardiotoxicity

*From Tian S et al. [6], with permission

BNP brain natriuretic peptide, *NT* N-terminal, *AC* anthracycline, *RT* radiation therapy, *HDC* high-dose chemotherapy, *T* trastuzumab, *LVEF* left ventricular ejection fraction, *HE* heart failure, *ALL* acute lymphoblastic leukemia, *FS* fractional shortening, *PFR* peak filling rate

It should be noted that NP, although broadly useful and predictive, must be interpreted within the entire clinical context at the moment of sampling for any given patient. For example, a rapid increase in BNP/NT-proBNP in a patient undergoing chemotherapy easily could be related to a concomitant process, such acute kidney injury or volume overload, without evidence of cardiac dysfunction or toxicity. In this context, the clinician is encouraged to make a careful assessment of the volume status of the patient and attempt to define the presence of other prominent comorbidity such as sepsis [39].

Troponin

Troponin I (TnI) and troponin T (TnT) are both cardiac specific proteins that form an integral part of the cardiac contractile unit [16, 22]. As biomarkers they are highly specific and sensitive for cardiac damage and are widely used in the diagnosis/treatment of acute coronary syndromes as currently supported by major guideline documents [40]. Elevations in troponin correlate with cardiac myocyte damage/death, however, it does not distinguish the mechanism of injury. As such, cardiac troponin has found utility in the screening of asymptomatic patients for cardiotoxicity during and after treatment [41–43]. A summary of the major clinical trials examining the utility of troponin in cardio-oncology is provided in Table 24.2 [6].

One of the larger studies to examine this topic enrolled 703 patients with various advanced malignances who were receiving high dose chemotherapy [41]. TnI was checked at initiation of therapy, and 1 month after. Cardiac function was measured and documented with echocardiography at baseline, and 1, 2, 6, and 12 months post therapy. Thirty percent of the patients had early TnI elevation, and a third of subsequently showed elevated TnI at 1 month. Reductions in ejection fraction were predicted by both early ($r = 0.78$, $p < 0.001$) and persistent elevation at 1 month ($r = 0.92$, $p < 0.001$). Not only did elevated troponin predict decline in EF, persistent elevation was able to predict the development of symptomatic HF which suggests that troponin elevation closely correlates with the cardiotoxic effects of the chemotherapeutic agents [44]. Having a positive troponin at any time predicted future cardiovascular events with a positive predictive value of 84 % and negative predictive value of 99 %. There is a suggestion that troponin I elevation may be able to predict cardiac dysfunction with other cardio-toxic therapy, such as trastuzumab, but the data has not been as consistent as initially reported [16, 45, 46]. Additionally, troponin T has shown utility in the care of patients with *light chain amyloidosis* [37, 38, 47]. Troponin levels are predictive of outcomes and decreases correlate with response to therapy and can be used to monitor disease activity in the post therapy patient with amyloidosis.

The utility of troponin to detect cardiac damage in patients who survived prior treatment of childhood cancer is a hopeful goal but has not been well established to date [48–50]. However, a study in patients with ALL treated with anthracyclines and dexrazoxane had a reduced incidence of elevated troponin underscoring the protec-

Table 24.2 Role of cardiac troponins in the evaluation of chemotherapy and radiation-induced cardiotoxicity*

Reference	Population	N	Treatment	Tn type	Cutoff	Troponin evaluations	Results and Conclusions
Hugh-Davies et al.	Breast cancer	50	ACs and RT	T	0.1 ng/ml	Pre- and post-treatment	No change in TnT after 45–46 Gy delivered to the whole breast
Lipshultz et al.	ALL	15	ACs	T	0.03 ng/ml	Baseline, and 1–3 days after each cycle	Correlation between TnT and LV end-diastolic dimension and wall thickness
Herman et al.	Animal study	37	ACs	T		Before, and 1 week after chemotherapy	TnT and histological myocardial changes in both related to cumulative doxorubicin dose
Cardinale et al.	Various	204	HDC	I	0.5 ng/ml	Before, and 0, 12, 24, 36, and 72 h after every cycle	Elevated TnI during treatment predicted for LVEF decline
Cardinale et al.	Breast cancer	211	HDC and RT	I	0.5 ng/ml	Before, and 0, 12, 24, 36, and 72 h after every cycle	Correlation between max TnI, number of positive assays, and max LVEF reduction
Auner et al.	Hematologic malignancies	78	ACs	T	0.03 ng/ml	Within 48 h of treatment start, then every 48 h during treatment	Correlation between TnT increase and median LVEF decline
Sandri et al.	Various	179	HDC		0.08 ng/ml	Before, and 0, 12, 24, 36, and 72 h after every cycle	TnI increase predicted subsequent LVEF decline
Cardinale et al.	Various	703	HDC	I	0.08 ng/ml	Before, and 0, 12, 24, 36, and 72 h after every cycle, and 1 month after treatment	Persistent TnI positivity predicted for subsequent LVEF decline
Kismet et al.	Pediatric solid cancers	24	ACs	T	0.01 ng/ml	With imaging, ›1 month after chemo	No relationship between TnT and echocardiographic abnormalities
Lipshultz et al.	**ALL**	76	ACs	T	0.01 ng/ml	Throughout chemotherapy	TnT persistencly increased suring treatment, and predicted for cardioprotective response
Kilickap et at	Various	41	ACs	T	0.01 ng/ml	Baseline, after first and last cycle	Correlation between TnT increase and diastolic dysfunction (E/A ratio)
Perik et al.	Breast cancer	17	ACs and T	I	0.1 g/1	Before, and throughout T	No TnI elevations in 15/16 patients

(continued)

Table 24.2 (continued)

Reference	Population	N	Treatment	Tn type	Cutoff	Troponin evaluations	Results and Conclusions
Dodos et al.	Various	100	ACs	T	0.1 ng/ml	After first dose, last does, and 1, 6, 12 months after last dose	No TnT elevations detected
Kozak et al. (72)	Lung and esophageal CA	30	ChemoRT	T		Baseline, 2 weeks after start of treatment and after	TnT undetectable in 20/30 patients
Cilt et al.	Breast cancer	33	ACs	I		Before and after chemotherapy	No correlation between Tnl and LVEF decline
Mavinkurve-Groothuis et al.	Various pediatric	122	ACs	T	0.01 ng/ml	Once, with imaging	No patients with elevated TnT levels
Cardinale et al.	Breast cancer	251	ACs and T	I	0.08 ng/ml	Before T, every 3 months during treatment, 1 year after start, every 6 months	Elevated Tnl values are an indepaendent predictor of cardiotocicity, and LVEF recovery
Nellessen et al.	Lung and breast CA	23	RT	I	0.03 ng/ml	Before RT, every week during RT for 4–6 weeks	Log-transformed Tnl increased during treatment
Fallah-Rad et al.	Breast cancer	42	ACs and T	T		Before chemotherapy, before T, and 3, 6, 9, and 12 months after start of T	No change in TNT values over time
Feola et al.	Breast cancer	53	ACs	I	0.03 ng/ml	Baseline, after 1 month, 1 and 2 years	Tnl concentrations elevated at 1 month, then returned to normal
Goel et al.	Breast cancer	36	ACs and T	I	0.20 ng/ml	Baseline, before and 24 h after T	No elevated Tnl values throughout
Morris et al.	Breast cancer	95	ACs and T	I	0.04—0.06 ng/ml	Every 2 weeks during treatment, then at 6, 9, and 18 months	Elevated Tnl values preceded maximal LVEF decline, but no relationship with max LVEF decline
Romano et al.	Breast cancer	92	ACs		5 or 0.08 ng/ml (age <50 or >50)	Every 2 weeks during treatment, then at 3, 6, and 12 months	No correlation between Tnl change and subsequent LV impairment

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Sawaya et al.	Breast cancer	43	ACs and T	I	0.015 ng/ml	Baseline, 3 and 6 months after chemotherapy	Elevated TnI at 3 months predicted for cardiotoxicity within 6 months
D'Errico et al.	Breast cancer	60	ChemoRT		0.07 ng/ml	Before and after RT	No elevated TnI concnetrations
Garrone et al.	Breast cancer	50	ACs	I	0.03 ng/ml	Baseline, 5, 16, and 28 months after	TnI kinetics correlated with LVEF decline
Lipshultz et al.	ALL	156	ACs		0.01 ng/ml	Before, and daily during induction, and after treatment	Lower incidence of detectable TnT during treatment with dexrazoxane
Onitilo et al.	Breast cancer	54	Taxanes and T	I	0.1 ng/ml	Baseline, and every 3 weeks during treatment	TnI undetectable throughout
Sawaya et al.	Breast cancer	81	ACs and T	I	30 pg/ml	Before, every 3 months during, and after T treatment	Elevated TnI values at end of treatment predictive of subsequent cardiotocitiy
Sherief et al.	Acute leukemias	50	ACs	T	0.01 ng/ml	Once, with imaging	No elevated TnT values
Erven et al.	Breast cancer	72	RT	I	0.13 ng/ml	Before and after RT	Higher TnI values in I-sided breast patients
Ky et al.	Breast cancer	78	ACs and T	I	121.8 ng/ml	Baseline, 3 and 6 months after start of chemotherapy	Interval change in TnI predicted cardiotoxicity

*From Tian et al. [6], with permission

Tn troponin, *AC* anthracycline, *RT* radiation therapy, *HDC* high-dose chemotherapy, T trastuzumab, *LVEE* left ventricular ejection fraction, *ALL* acute lymphoblastic leukemia

tive effect during active treatment [31]. In another study elevated troponin correlated with lower LV mass at 4 years post treatment [44]. Although early troponin elevation during therapy was predictive of cardiac dysfunction, post therapy troponin did not correlate with risk of late onset cardiotoxicity [48].

Despite the utility of troponin as outlined above, there appears to be mixed data as it relates to the utility of troponin levels for predicting radiation induced cardiomyopathy [51, 52].

Emerging Biomarkers

There has been a desire to identify an effective biomarker to detect cardiac injury during cancer treatment and therefore other markers have been investigated.

Myeloperoxidase (MPO)

MPO is a proatherogenic enzyme produced by neutrophils that is indicative off oxidative stress and lipid peroxidation. Its prognostic role in acute coronary syndrome and heart failure has been suggested [46, 53–55]. In the context of cancer chemotherapy, a panel of biomarkers including NT-proBNP, growth differentiation factor (GDF)-15, placenta growth factor (PlGF), c reactive protein (crp), soluble fms-like tyrosine kinase receptor (sFlt)-1, and galectin (gal)-3 in breast cancer patients receiving antracyclines and herceptin were examined [46]. In patients with 90th percentile MPO interval change from baseline the probability of cardiotoxicity at 15 months was 34.2 %, and the risk of future cardiac toxicity increased with each standard deviation increase in MPO concentration (HR 1.34, $p = 0.048$). Although, the most useful biomarker tested was high sensitivity troponin I, MPO was also modestly useful in detection of cardiac damage.

C-reactive Protein (CRP)

CRP is an acute phase reactant produced in response to inflammation [56, 57]. Although its role in CAD and HF is well documented, the utility of CRP in the cardio-oncology patient population has mixed results [58, 59]. High-sensitivity CRP (hsCRP) concentrations ≥3 mg/l predicted impaired LVEF with 92.9 % sensitivity and 45.7 % specificity (PPV, 40.6 %; NPV, 94.1 %) in a cohort of breast cancer patients. HsCRP elevations occurred >70 days before echocardiographic changes were seen. As such, hsCRP maybe able to risk stratify patients and delineate who needs more stringent follow up [58]. Another study, in a survivorship cohort, found higher CRP values regardless of exposure to cardiotoxic treatment but poor correlation with LV mass,

wall thickness, and dimension [50]. This suggests that hs-CRP may be a surrogate for overall inflammation or tumor burden in addition to drug effects.

Total Antioxidant Status (TAOS)

Total antioxidant status is a sum total of antioxidants in the blood and could potentially be used to monitor for cardiac toxicity in anthracycline based therapy [49]. A study of 29 children undergoing anthracycline based therapy for acute leukemia showed statistically significant decrease in TAOS which correlated with higher total doses of anthracyclines and subsequent reduction in LVEF.

Nitric Oxide (NO)

NO is generated by NO synthase from L-arginine in numerous cell types and is a key regulator of cardiomyocyte contractility [60]. Dysregulated NO synthesis is implicated in the pathophysiology of doxorubicin-induced cardiotoxicity [6, 60]. One study demonstrated significantly higher plasma levels of total nitrite, a stable product of NO, in children that received doxorubicin and in those with abnormal LVEF as compared to healthy controls and an increased NO may be an indicator of subclinical cardiotoxicity.

In addition to the markers discussed above, future directions include heart-type fatty acid-binding protein, cytochrome C, glycogen phosphorylase isoenzyme BB and circulating microRNAs deserve mention as potential targets.

Conclusion

With a dramatic improvement in the overall survival and outcomes of patients with cancer, cardiac damage or exacerbation of underlying cardiac disease by cancer therapy has become a critically important issue for cancer survivors and clinicians. Screening for cardiotoxicity, as per current guidelines, focuses predominantly on serial noninvasive imaging. This is costly, subject to variation in reader interpretation, and often detects changes when cardiac remodeling has already taken place. Cardiac biomarkers have emerged as an inexpensive means to serially follow patients and to potentially detect early subclinical cardiac toxicity. Biomarkers can delinate low versus high risk patients allowing for intensive screening in the later group. As such, biomarkers, can potentially reduce costs associated with unnecessary serial screening. Early, detection of subclinical cardiotoxic effects, facilitate changes in the chemotherapy regimen and/or the initiation of cardioprotective medical regimen (eg. Beta blocker) to prevent permanent cardiac remodeling.

In summary, biomarkers offer significant advantages in the detection, treatment and prognostication of cardiotoxicity. Multiple cardiac biomarkers have been studied and shown utility in this setting. However, as we look to the future with ever increasing array of available chemotherapy agents, further prospective randomized trials need to be conducted with the incorporation of cardiac biomarkers to improve our understanding of their optimal role. Eventually, cardiac biomarkers maybe implemented in every day practice and serve to replace or complement cardiac imaging.

Here we will present a patient recently seen at our medical center and illustrate how we applied biomarkers to their medical care.

Case

A 65 y/o Caucasian male, WL, with medical history of hypertension and dyslipidemia was referred to our heart failure clinic from an outside general cardiology clinic for evaluation of difficult to manage heart failure with preserved ejection fraction (HFpEF). Despite diuretic therapy, he continued to have orthopnea, edema and dyspnea with minimal activity. His echocardiogram showed mild concentric LVH, normal ejection fraction, grade II diastolic dysfunction and no significant valvular pathology. His electrocardiogram showed low voltage and a pseudoinfarct pattern raising suspicion for infiltrative cardiomyopathy. Laboratory evaluation showed a monoclonal protein spike and a bone marrow biopsy was notable for 15 % clonal plasma cells and no amyloid. A cMRI demonstrated global subendocardial delayed enhancement consistent with amyloidosis. A cardiac catheterization was negative for significant coronary disease with biopsy positive for congo red staining- confirming a diagnosis of AL cardiac amyloidosis. His diuretic regimen was adjusted and with careful attention to salt/fluid intake his HFpEF symptoms improved.

He was referred to the Oncology clinic for further evaluation. At that point his troponin I was 0.12 ng/ml (<0.03 ng/ml), BNP 569 pg/ml (<100 pg/ml) and serum lamda light chain 27.19 mg/dl (0.57-2.63 mg/dl). At this point he was started on induction therapy with 6 cycles of bortezomib and dexamethasone. During induction therapy he developed worsening heart failure symptoms and a repeat echocardiogram showed ejection fraction of 35 %. His troponin I and BNP increased to 0.21 ng/ml and 1006 pg/ml respectively. His cardiac dysfunction was presumed secondary to bortezomib. Based on prior reported studies this is generally reversible [52]. We adjusted his medical regimen with the addition of carvedilol, spironolactone and uptitration of his diuretic regimen. We continued and completed induction therapy. After approximately 6 months his LVEF was back to normal. Additionally, troponin I and BNP decreased to 0.13 ng/ml and 340 pg/ml respectively, signally cardiac recovery and reduction in disease activity. He subsequently underwent consolidation therapy with reduced dose melphalan and stem cell transplantation. During post-transplant follow up, troponin I normalized, BNP decreased to

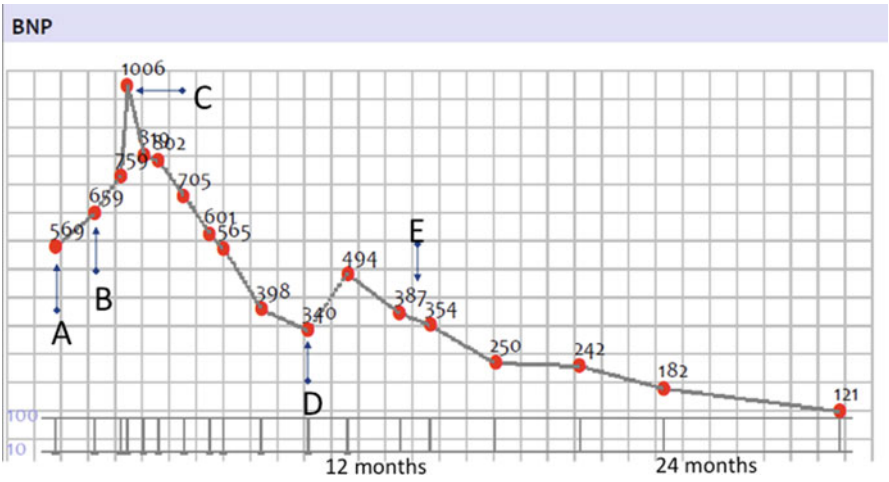

Fig. 24.1 The time course of BNP elevation (pg/ml) during the diagnosis and successful treatment of a patient with AL amyloidosis. (*A*) diagnosis, (*B*) bortezomib + dexamethasone, (*C*) LVEF drop to 35 %, (*D*) LVEF recovery/stem cell transplant, (*E*) heart failure symptoms improved

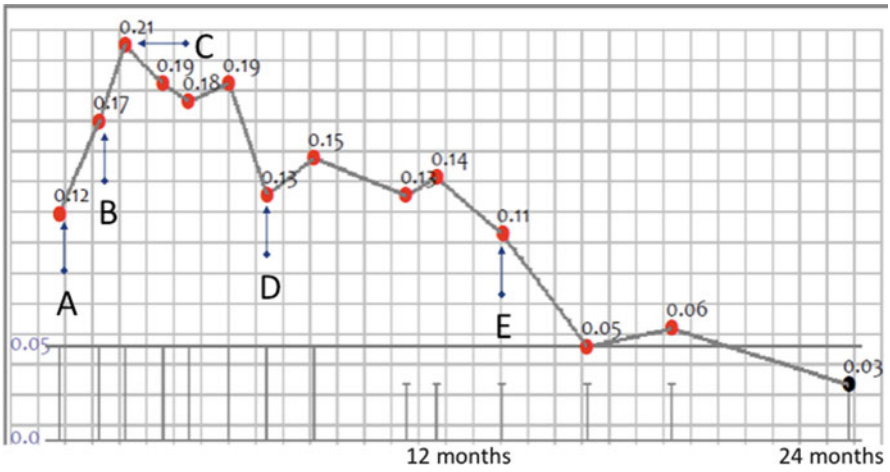

Fig. 24.2 The time course of Troponin I elevation (ng/ml) during the diagnosis and successful treatment of a patient with AL amyloidosis. (*A*) diagnosis, (*B*) chemotherapy + dexamethasone, (*C*) LVEF drop to 35 %, (*D*) LVEF recovery/stem cell transplant, (*E*) heart failure symptoms improved

120 pg/ml and serum lambda light chain decreased to the normal range <1.66 mg/dl. Overall, the biomarker activity was consistent with no amyloid disease activity and no ongoing cardiac damage. We will continue to follow him closely checking BNP and troponin levels periodically (Figs. 24.1, 24.2, and 24.3).

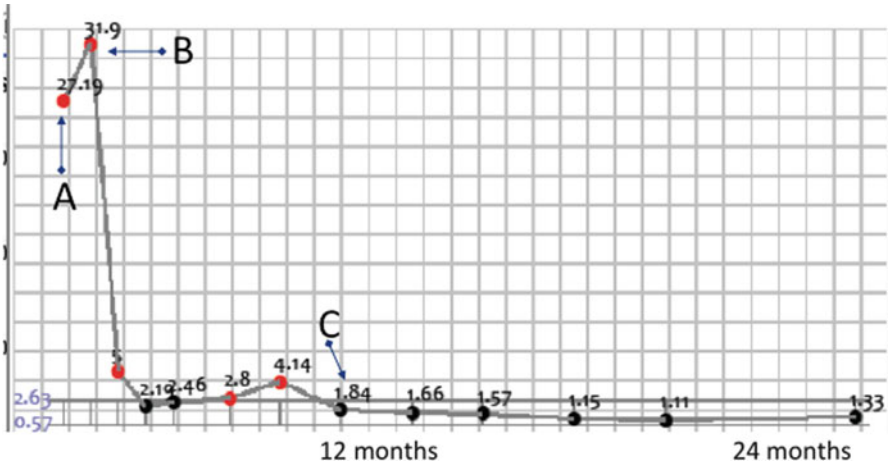

Fig. 24.3 The time course of lambda light chain levels (mg/dl) during the diagnosis and successful treatment of a patient with AL amyloidosis. (*A*) diagnosis, (*B*) chemotherapy + dexamethasone, (*C*) heart failure symptoms improved

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