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PHARMACOLOGIC THERAPY (W H W TANG, SECTION EDITOR)

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 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

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Introduction

With advances in cancer research, highly efficacious anticancer chemotherapeutic regiments are now a reality. However, this has come at a price of significant cardiotoxicity, particularly in the era of the increase in the number of long-term cancer survivors. The incidence of cardiotoxicity varies by the chemotherapeutic agent used but generally 5–20 % for asymptomatic decrease in left ventricular ejection fraction (LVEF) to 1 to 5 % 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 individualized chemotherapy regimens and therapeutic options to prevent irreversible cardiac dysfunction.

Anthracycline chemotherapy (AC) regiments 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 % in patients receiving a cumulative dose of 3–5 % in 400 mg/m^2 to 18–48 % in patients receiving more than 700 mg/m^2 [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]. Rechallenging 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 the group of tyrosine kinase inhibitors on vascular endothelial growth factor (VEGF) receptors and HER-2 receptors.

Current recommendations for monitoring of the functional capacity of the heart in chemotherapy patients is performed by evaluating the left ventricular ejection fraction (LVEF) by either transthoracic echocardiography or radionuclide ventriculography, with specific time points depending on the 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 are 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 cardio-specific 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].

Their 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 was 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, cTnI positivity was found to be predictive of greater decrease in LVEF at 1 month of 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 (1 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 %. 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-Hodgkin's 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 ultrasensitive 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 % of longitudinal strain had a 95 % specificity for development of cardiotoxicity. In this cohort, parameters of diastolic dysfunction as well as N-terminal pro brain natriuretic peptides (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 were found to correlate with parameters of diastolic dysfunction [23].

There is established literature regarding the use of dexrazoxane, angiotensin-converting enzyme (ACE) inhibitors, and beta blockers to be beneficial in treating or

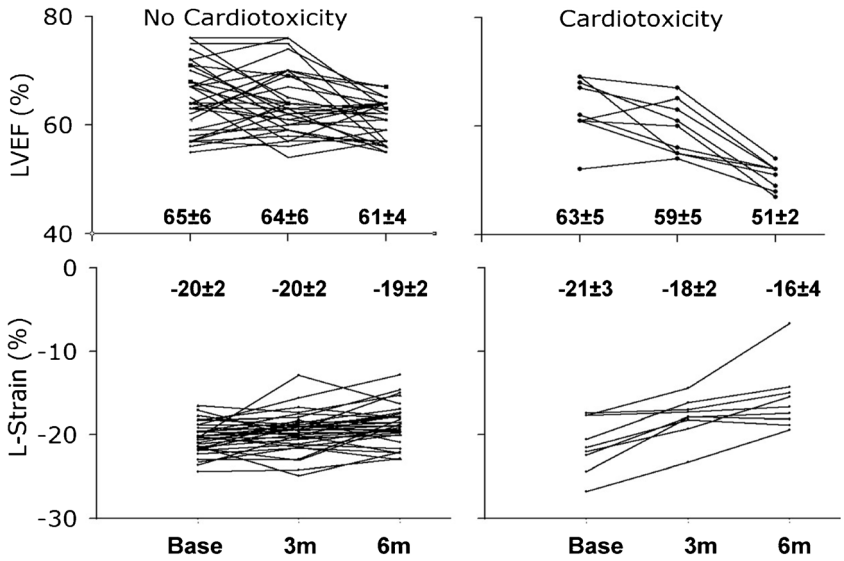

Fig. 1 Individual changes in the LVEF (*top*) and longitudinal strain (*bottom*) in patients who did not develop (*left*) and those who developed (*right*) cardiotoxicity [21]. *Permission obtained*

preventing chemotherapy-induced cardiomyopathy [24–26]. In 50 patients with acute lymphoblastic leukemia (ALL) receiving AC cardiotoxicity, El-Shitany et al. demonstrated that the group of patients randomized to receive carvedilol 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, N-terminal pro BNP (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 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 end point (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 h after every cycle of HDC with echocardiograms obtained before HDC, monthly for 3 months, and three monthly for the first 2 years [15]. Most cTnI positivity occurred soon after the end of drug administration, and there was evidence of LVEF reduction from 3 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 2.5–5 mg/day, and in patients receiving at least 5 mg/day of enalapril, 6.25 mg/day of carvedilol 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 illustrating 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 that in 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/m^2) were 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-year 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 concominant decrease in LVEF. In two other series of 29 and 31 patients undergoing anthracycline therapy for heme malignancies, cTnI was measured once, 1 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 the 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. Sixty-four percent 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

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 h after initiation of chemotherapy, then every 48 h afterwards until discharge. This process was 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, 12, 24, 36, and 72 h 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, 12, 24, 36, and 72 h 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, 12, 24, 36, and 72 h after each cycle of HDC 1 month after the last cycle	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
Kilickap 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 are associated with diastolic dysfunction
Morris et al., 2011 [34]	Breast cancer patients treated with dose-dense chemotherapy incorporating trastuzumab and lapatinib	95	I	Baseline, every 2 weeks during chemotherapy, then at 6, 6 and 18 months	cTnI 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

each patient. They found cardiac dysfunction in three 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 six 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 and 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 homogenously 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 the following: 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.

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 12 h In 19 % after 24 h In 7 % after 36 h In 12 % after 72 h 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 12 h 25 % at 24 h 10 % at 36 h 13 % at 72 h 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 h 8 % after 24 h 24 % after 36 h 13 % after 72 h
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
Kilickap., 2005 [23]	2 had inc. after first cycle (3–5 days 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

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 h 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 the decline in ejection fraction and development of clinical heart failure [50].

Data with BNP levels in patients receiving trastuzumab therapy is less clear. Higher pretreatment 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 ten 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, galectin-3, and soluble fms-like tyrosine kinase receptor, increases of MPO and troponin I when measured 3 months were 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.

Compliance with Ethics Guidelines

Conflict of Interest Dhssraj Singh, Akanksha Thakur, and W. H. Wilson Tang declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

1. Shakir DK, Rasul KI. Chemotherapy induced cardiomyopathy: pathogenesis, monitoring and management. J Clin Med Res. 2009;1(1):8–12.
2. Curigliano G, Cardinale D, Suter T, Plataniotis G, de Azambuja E, Sandri MT, et al. Cardiovascular toxicity induced by chemotherapy, targeted agents and radiotherapy: ESMO clinical practice guidelines. Ann Oncol. 2012;23 Suppl 7:vii155–66.
3. Minotti G, Menna P, Salvatorelli E, Cairo G, Gianni L. Anthracyclines: molecular advances and pharmacologic developments in antitumor activity and cardiotoxicity. Pharmacol Rev. 2004;56(2):185–229.
4. Ewer MS, Vooletich MT, Durand JB, Woods ML, Davis JR, Valero V, et al. Reversibility of trastuzumab-related cardiotoxicity: new insights based on clinical course and response to medical treatment. J Clin Oncol. 2005;23(31):7820–6.
5. Cheitlin MD, Armstrong WF, Aurigemma GP, Beller GA, Bierman FZ, Davis JL, et al. ACC/AHA/ASE 2003 guideline update for the clinical application of echocardiography: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASE Committee to Update the 1997 Guidelines for the Clinical Application of Echocardiography). Circulation. 2003;108(9):1146–62.
6. Panteghini M. Role and importance of biochemical markers in clinical cardiology. Eur Heart J. 2004;25(14):1187–96.
7. Antman EM, Tanasijevic MJ, Thompson B, Schactman M, McCabe CH, Cannon CP, et al. Cardiac-specific troponin I levels to predict the risk of mortality in patients with acute coronary syndromes. N Engl J Med. 1996;335(18):1342–9.
8. Konstantinides S, Geibel A, Olschewski M, Kasper W, Hruska N, Jackle S, et al. Importance of cardiac troponins I and T in risk stratification of patients with acute pulmonary embolism. Circulation. 2002;106(10):1263–8.
9. Horwich TB, Patel J, MacLellan WR, Fonarow GC. Cardiac troponin I is associated with impaired hemodynamics, progressive left ventricular dysfunction, and increased mortality rates in advanced heart failure. Circulation. 2003;108(7):833–8.
10. Adamcova M, Sterba M, Simunek T, Potacova A, Popelova O, Mazurova Y, et al. Troponin as a marker of myocardiac damage in drug-induced cardiotoxicity. Expert Opin Drug Saf. 2005;4(3):457–72.
11. Herman EH, Zhang J, Lipshultz SE, Rifai N, Chadwick D, Takeda K, et al. Correlation between serum levels of cardiac troponin-T and the severity of the chronic cardiomyopathy induced by doxorubicin. J Clin Oncol. 1999;17(7):2237–43.
12. Adamcova M, Gersl V, Hrdina R, Melka M, Mazurova Y, Vavrova J, et al. Cardiac troponin T as a marker of myocardial damage caused by antineoplastic drugs in rabbits. J Cancer Res Clin Oncol. 1999;125(5):268–74.
13. Koh E, Nakamura T, Takahashi H. Troponin-T and brain natriuretic peptide as predictors for adriamycin-induced cardiomyopathy in rats. Circ J: Off J Jpn Circ Soc. 2004;68(2):163–7.
14. Cardinale D, Sandri MT, Martinoni A, Tricca A, Civelli M, Lamantia G, et al. Left ventricular dysfunction predicted by early troponin I release after high-dose chemotherapy. J Am Coll Cardiol. 2000;36(2):517–22.
15. Cardinale D, Colombo A, Lamantia G, Colombo N, Civelli M, De Giacomi G, et al. Anthracycline-induced cardiomyopathy: clinical relevance and response to pharmacologic therapy. J Am Coll Cardiol. 2010;55(3):213–20.
16. Cardinale D, Sandri MT, Martinoni A, Borghini E, Civelli M, Lamantia G, et al. Myocardial injury revealed by plasma troponin I in breast cancer treated with high-dose chemotherapy. Ann Oncol. 2002;13(5):710–5.
17. Sandri MT, Cardinale D, Zorzino L, Passerini R, Lentati P, Martinoni A, et al. Minor increases in plasma troponin I predict decreased left ventricular ejection fraction after high-dose chemotherapy. Clin Chem. 2003;49(2):248–52.

18. Cardinale D, Sandri MT, Colombo A, Colombo N, Boeri M, Lamantia G, et al. Prognostic value of troponin I in cardiac risk stratification of cancer patients undergoing high-dose chemotherapy. Circulation. 2004;109(22):2749–54.
19. Auner HW, Tinchon C, Linkesch W, Tiran A, Quehenberger F, Link H, et al. Prolonged monitoring of troponin T for the detection of anthracycline cardiotoxicity in adults with hematological malignancies. Ann Hematol. 2003;82(4):218–22.
20. Kang Y, Xu X, Cheng L, Li L, Sun M, Chen H, et al. Two-dimensional speckle tracking echocardiography combined with high-sensitive cardiac troponin T in early detection and prediction of cardiotoxicity during epirubicine-based chemotherapy. Eur J Heart Fail. 2014;16(3):300–8.
21. Sawaya H, Sebag IA, Plana JC, Januzzi JL, Ky B, Cohen V, et al. Early detection and prediction of cardiotoxicity in chemotherapy-treated patients. Am J Cardiol. 2011;107(9):1375–80.
22. Sawaya H, Sebag IA, Plana JC, Januzzi JL, Ky B, Tan TC, et al. Assessment of echocardiography and biomarkers for the extended prediction of cardiotoxicity in patients treated with anthracyclines, taxanes, and trastuzumab. Circ Cardiovasc Imaging. 2012;5(5):596–603.
23. Kilickap S, Barista I, Akgul E, Aytemir K, Aksoyek S, Aksoy S, et al. cTnT can be a useful marker for early detection of anthracycline cardiotoxicity. Ann Oncol. 2005;16(5):798–804.
24. El-Shitany NA, Tolba OA, El-Shanshory MR, El-Hawary EE. Protective effect of carvedilol on adriamycin-induced left ventricular dysfunction in children with acute lymphoblastic leukemia. J Card Fail. 2012;18(8):607–13.
25. Kalay N, Basar E, Ozdogru I, Er O, Cetinkaya Y, Dogan A, et al. Protective effects of carvedilol against anthracycline-induced cardiomyopathy. J Am Coll Cardiol. 2006;48(11):2258–62.
26. Noori A, Lindenfeld J, Wolfel E, Ferguson D, Bristow MR, Lowes BD. Beta-blockade in adriamycin-induced cardiomyopathy. J Card Fail. 2000;6(2):115–9.
27. Goel S, Simes RJ, Beith JM. Exploratory analysis of cardiac biomarkers in women with normal cardiac function receiving trastuzumab for breast cancer. Asia Pac J Clin Oncol. 2011;7(3):276–80.
28. Cardinale D, Colombo A, Sandri MT, Lamantia G, Colombo N, Civelli M, et al. Prevention of high-dose chemotherapy-induced cardiotoxicity in high-risk patients by angiotensin-converting enzyme inhibition. Circulation. 2006;114(23):2474–81.
29. Cadeddu C, Piras A, Mantovani G, Deidda M, Dessi M, Madeddu C, et al. Protective effects of the angiotensin II receptor blocker telmisartan on epirubicin-induced inflammation, oxidative stress, and early ventricular impairment. Am Heart J. 2010;160(3):487. **e1-7**.
30. Nakamae H, Tsumura K, Terada Y, Nakane T, Nakamae M, Ohta K, et al. Notable effects of angiotensin II receptor blocker, valsartan, on acute cardiotoxic changes after standard chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisolone. Cancer. 2005;104(11):2492–8.
31. Jensen BV, Skovsgaard T, Nielsen SL. Functional monitoring of anthracycline cardiotoxicity: a prospective, blinded, long-term observational study of outcome in 120 patients. Ann Oncol. 2002;13(5):699–709.
32. Bosch X, Rovira M, Sitges M, Domenech A, Ortiz-Perez JT, de Caralt TM, et al. Enalapril and carvedilol for preventing chemotherapy-induced left ventricular systolic dysfunction in patients with malignant hemopathies: the OVERCOME trial (prevention of left ventricular dysfunction with enalapril and carvedilol in patients submitted to intensive chemotherapy for the treatment of malignant hemopathies). J Am Coll Cardiol. 2013;61(23):2355–62.
33. Tallaj JA, Franco V, Rayburn BK, Pinderski L, Benza RL, Pamboukian S, et al. Response of doxorubicin-induced cardiomyopathy to the current management strategy of heart failure. J Heart Lung Transplant: Off Pub Int Soc Heart Transplant. 2005;24(12):2196–201.
34. Morris PG, Chen C, Steingart R, Fleisher M, Lin N, Moy B, et al. Troponin I and C-reactive protein are commonly detected in patients with breast cancer treated with dose-dense chemotherapy incorporating trastuzumab and lapatinib. Clin Cancer Res: Off J Am Assoc Cancer Res. 2011;17(10):3490–9.
35. Octavia Y, Tocchetti CG, Gabrielson KL, Janssens S, Crijns HJ, Moens AL. Doxorubicin-induced cardiomyopathy: from molecular mechanisms to therapeutic strategies. J Mol Cell Cardiol. 2012;52(6):1213–25.
36. Lipshultz SE, Rifai N, Dalton VM, Levy DE, Silverman LB, Lipsitz SR, et al. The effect of dexrazoxane on myocardial injury in doxorubicin-treated children with acute lymphoblastic leukemia. N Engl J Med. 2004;351(2):145–53.
37. Marty M, Espie M, Llombart A, Monnier A, Rapoport BL, Stahalova V, et al. Multicenter randomized phase III study of the cardioprotective effect of dexrazoxane (Cardioxane) in advanced/metastatic breast cancer patients treated with anthracycline-based chemotherapy. Ann Oncol. 2006;17(4):614–22.
38. Lipshultz SE, Scully RE, Lipsitz SR, Sallan SE, Silverman LB, Miller TL, et al. Assessment of dexrazoxane as a cardioprotectant in doxorubicin-treated children with high-risk acute lymphoblastic leukaemia: long-term follow-up of a prospective, randomised, multicentre trial. Lancet Oncol. 2010;11(10):950–61.
39. Choi HS, Park ES, Kang HJ, Shin HY, Noh CI, Yun YS, et al. Dexrazoxane for preventing anthracycline cardiotoxicity in children with solid tumors. J Korean Med Sci. 2010;25(9):1336–42.
40. Dodos F, Halbsguth T, Erdmann E, Hoppe UC. Usefulness of myocardial performance index and biochemical markers for early detection of anthracycline-induced cardiotoxicity in adults. Clin Res Cardiol. 2008;97(5):318–26.
41. Erkus B, Demirtas S, Yarpuzlu AA, Can M, Genc Y, Karaca L. Early prediction of anthracycline induced cardiotoxicity. Acta Paediatr. 2007;96(4):506–9.
42. Soker M, Kervancioglu M. Plasma concentrations of NT-pro-BNP and cardiac troponin-I in relation to doxorubicin-induced cardiomyopathy and cardiac function in childhood malignancy. Saudi Med J. 2005;26(8):1197–202.
43. Kismet E, Varan A, Ayabakan C, Alehan D, Portakal O, Buyukpamukcu M. Serum troponin T levels and echocardiographic evaluation in children treated with doxorubicin. Pediatr Blood Cancer. 2004;42(3):220–4.
44. Koseoglu V, Berberoglu S, Karademir S, Kismet E, Yurttutan N, Demirkaya E, et al. Cardiac troponin I: is it a marker to detect cardiotoxicity in children treated with doxorubicin? Turk J Pediatr. 2005;47(1):17–22. **Jan-Mar**.
45. Fallah-Rad N, Walker JR, Wassef A, Lytwyn M, Bohonis S, Fang T, et al. The utility of cardiac biomarkers, tissue velocity and strain imaging, and cardiac magnetic resonance imaging in predicting early left ventricular dysfunction in patients with human epidermal growth factor receptor II-positive breast cancer treated with adjuvant trastuzumab therapy. J Am Coll Cardiol. 2011;57(22):2263–70.
46. Jensen KT, Carstens J, Pedersen EB. Effect of BNP on renal hemodynamics, tubular function and vasoactive hormones in humans. Am J Phys. 1998;274(1 Pt 2):F63–72.
47. Dao Q, Krishnaswamy P, Kazanegra R, Harrison A, Amirnovin R, Lenert L, et al. Utility of B-type natriuretic peptide in the diagnosis of congestive heart failure in an urgent-care setting. J Am Coll Cardiol. 2001;37(2):379–85.
48. Berger R, Huelsman M, Strecker K, Bojic A, Moser P, Stanek B, et al. B-type natriuretic peptide predicts sudden death in patients with chronic heart failure. Circulation. 2002;105(20):2392–7.
49. Romano S, Fratini S, Ricevuto E, Procaccini V, Stifano G, Mancini M, et al. Serial measurements of NT-proBNP are predictive of not-

high-dose anthracycline cardiotoxicity in breast cancer patients. Br J Cancer. 2011;105(11):1663–8.

50. Kouloubinis A, Kaklamanis L, Ziras N, Sofroniadou S, Makaritsis K, Adamopoulos S, et al. ProANP and NT-proBNP levels to prospectively assess cardiac function in breast cancer patients treated with cardiotoxic chemotherapy. Int J Cardiol. 2007;122(3): 195–201.
51. Perik PJ, Lub-De Hooge MN, Gietema JA, van der Graaf WT, de Korte MA, Jonkman S, et al. Indium-111-labeled trastuzumab scintigraphy in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer. J Clin Oncol. 2006;24(15): 2276–82.
52. Ky B, Putt M, Sawaya H, French B, Januzzi Jr JL, Sebag IA, et al. Early increases in multiple biomarkers predict subsequent cardiotoxicity in patients with breast cancer treated with doxorubicin, taxanes, and trastuzumab. J Am Coll Cardiol. 2014;63(8): 809–16.
53. Lipshultz SE, Miller TL, Scully RE, Lipsitz SR, Rifai N, Silverman LB, et al. Changes in cardiac biomarkers during doxorubicin treatment of pediatric patients with high-risk acute lymphoblastic leukemia: associations with long-term echocardiographic outcomes. J Clin Oncol. 2012;30(10):1042–9.