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Diagnostic Strategies of Cancer Therapeutics-Related Cardiac Dysfunction [Version 1, Awaiting Peer Review]

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Abstract

Cardiac toxicity in the shape of heart malfunction maintains to be a trammel for patients with cancer. Morbidity and mortality of patients with cancer often influence by remained incidence of cardiac disease. The inclusion of the cardiac system by malignancies, alongside its dysfunction secondary to the management of antineoplastic drugs, has caused the development of a new discipline called Cardio-Oncology, it is a new cardiology sub-branch with more questions than answers and eventually an enormous opportunity for research in the field.Multidisciplinary efforts have focused on the prevention, diagnosis, and treatment of cancer therapeutics–related cardiovascular dysfunction (CTRCD). This review article will focus on the diagnosis of left ventricular dysfunction associated with chemotherapy by cardiac biomarkers. At present, the identification of cardiac toxicity associated with cancer treatment is the cornerstone for critical decisions regarding anticancer therapy and cardio protective strategies. Its determination permits prepared intervention to hinder further deterioration of the myocardium and different cardiac structures. We investigated the current evidence and recommendations for biochemical, including their particular role for identification of CTRCD. Cardiovascular biomarkers used alone or in combination with traditional and advanced imaging modalities are underlying the identification of cardiac toxicity during treatment. Core and clinical researchers are focused on the development of more sensitive and specific diagnostic means and for the recognition of cardiac toxicity.

Keywords

Cardiomyopathy; Chemotherapy; Cardiotoxicity

Introduction

Recent advancements in chemotherapy have improved outcomes of malignancies improving survival and allowing patients to have hopes for the cure and better quality of life. However, cancer therapeutics–related cardiac dysfunction (CTRCD) is emerging as one of the leading causes of morbidity and mortality among cancer survivors [1,2].The most common manifestations of cardiotoxicity secondary to chemotherapy include the subclinical decline of left ventricular ejection fraction (LVEF),new-onset heart failure, conduction disorders, hypertension, thrombotic events, and cardiovascular ischemia [3]. Although many chemotherapeutic drugs such as cyclophosphamide, 5-fluorouracil, and vincristine in high doses associated with CTRCD, the two best characterized by drugs associated with CTRCD are anthracycline and trastuzumab.Although the mechanisms by which these drugs cause cardiotoxicity are not entirely understood, it is believed they work in different ways. Anthracycline increases oxidative stress leading to loss of myofibrils and vacuolization of the myocytes. [4]; it also blocks topoisomerase II enzymes by intercalating with double-stranded DNA, leading to breaks in DNA that cause apoptosis of cardiomyocytes. These effects are cumulative and dose dependent and view as irreversible [5]. The estimated percentage of cardiomyopathy is 3% to 5% at a cumulative dose of 400 mg/m2, 7% to 26% at 550 mg/m2, and 18% to 48% at 70 mg/m2 [6]. Trastuzumab blocks ErB2 signaling and affects cardiomyocytes in a not–dose dependent manner but increases incidence of heart failure when used along with other agents. The impact of heart failure of trastuzumab alone can reach 7% when used as monotherapy and increases to 27% when used with anthracyclines or other agents such as paclitaxel and cyclophosphamide. However, unlike anthracycline, the effects are usually reversible and cardiac function typically improves to baseline after discontinuation of the drug [3,7]. Methods for detection of subclinical cardiac injury are useful for selecting individuals who might benefit from therapeutic interventions to prevent further deterioration in left ventricular (LV) function with progression to subsequent cardiovascular events [8,9]. The cornerstone for evaluating CTRCD is the use of noninvasive imaging techniques to assess the LV systolic function displacing cardiac biopsy as the preferred method. According to the last expert opinion, as well as the European Task Force, CTRCD describes as a decrease in LVEF >10% to a value of <53% (or the lower limit of nor mality) with a repeat performed 2 to 3 weeks after the initial decrease observe [9,10]. A potential alternative to the detection of CTRCD is the measurement of cardiac biomarkers. This diagnostic approach may allow for early detection of heart toxicity and can offer an opportunity to provide interventions to reduce the risk of permanent cardiac dysfunction or subsequent cardiovascular events [9]. Some potential benefits of using biomarkers as a screening tool are that this strategy is easier to perform, noninvasive, cheaper, and reliable. The biomarkers that have studied include cardiac troponin, B-type natriuretic peptide (BNP), C-reactive protein, and myeloperoxidase (MPO).

Troponin

Cardiac troponin is the gold standard biomarker in the assessment of myocyte damage, with both high diagnostic and prognostic value. It plays a major role in the diagnosis of acute coronary syndrome and myocardial damage [11] as it is let out into the bloodstream during processes of myocardial cell disruption. It is fixed on the actin filament of myocytes and is basic for calcium-mediated cardiac muscle contraction. New advancements in troponin assays have remained the sensitivity of the biomarker to represent cardiomyocyte damage with high sensitivity and specificity. Patients with elevation of troponins receiving doxorubicin Lipshultz et al. first identified chemotherapy in children who were receiving treatment for acute lymphoblastic leukemia [12]. Since then, multiple studies have documented the role of this biomarker in patients undergoing cancer treatment. Another prospective study by the same group found out important cardiac abnormalities in children who had at least one elevated troponin during treatment [13]. Another group examined the utility of using early troponin measurements for predicting future cardiotoxicity [14–17]. They certified a bare association between the pattern of troponin elevation and cardiac prognosis. Patients undergoing high-dose therapy for several malignancies and who had negative troponins had no important attenuation in LVEF, demonstrating negative predictive value.On the contrary, patients with early elevations in troponin had a reduction of LV function and cardiac events of 37%, and those with positive biomarkers had and the incidence of cardiac events of 84% [16]. After all, studies investigating troponin in the setting of trastuzumab use are less well identified, and their results are less consistent with one another. In a study, measured troponins in 251 patient treated for breast cancer with trastuzumab by Cardinale.They demonstrated that CTRCD happened more often in patients with either baseline raised troponin or elevations during treatment. Also, it was the only independent predictor of CTRCD and lack of LVEF recovery. In total, 60% of the women who improved LVEF dysfunction fully saved after withdrawal of trastuzumab [18]. On the contrary, different studies have demonstrated no remain troponin level after 12 months of follow-up in patients treated with trastuzumab for breast cancer [19]; likewise, other investigators found that significant troponin increase in the setting of trastuzumab treatment principal happened in patients who had been treated once with anthracyclines or when trastuzumab gives in combination with another cardiotoxic agents [20]. Besides, a study demonstrated upregulation of myocardial HER2 (ErbB2) expression briefly after therapy with anthracycline, likely as compensatory mechanism based on cardiac exposure to oxidative stress [21]. The patterns in troponin elevation in acute myocardial infarction and catecholamine-induced cardiomyopathy are completely varied, and it is, thus, irrational to appropriate either model for CTRCD [16,22,23]. In a study examined the interrelation between anthracycline infusion, the pattern of troponin level elevation, and their correlation with CTRCD [24]. Cardiotoxicity induced by infusing daunorubicin in an animal study. It indicated that late and persistent troponin

release in the setting of daunorubicin had a powerful intercorrelation with LV systolic dysfunction.

B-Type Natriuretic Peptide

B-type natriuretic peptide produces in return for increased wall stretch and plays a significant role in diagnose of heart failure with reduced and preserved ejection fraction (EF). N-terminal pro-BNP is an inactive protein of the BNP molecule that is cleaved from pro-BNP to release BNP. A study involving 12 anthracycline-treated breast cancer patients with a cumulative dosage of >220 mg/m2 and with BNP >100 mg/mL was predictive of the development of heart failure [25]. Two other studies demonstrated that regularly elevated levels of NT-proBNP for more than 72 hours were also predictive of LV impairment at 12-month follow-up with the mean LVEF was decreasing from 62.8% to 45.6% [26,27]. In a larger study of 333 patients treated with anthracyclines, BNP was found to be an independent predictor of the development of congestive heart failure and overall mortality [28]. Despite this evidence, the utility of BNP as a biomarker for CTRCD remains in question due to conflicting information, with several other studies showing no relationship and little prognostic value [19,29]. There are several challenges in using BNP as a biomarker. First, natriuretic peptide levels serve as reasonable surrogates for both LV dysfunction and the cumulative dose of anthracyclines [30,31]. Therefore, it is questionable whether BNP is just a marker for exposure to anthracyclines rather than right cardiotoxicity. Also, natriuretic peptides can be an unreliable biomarker as they tend to be influenced by age, gender, and other factors, including renal dysfunction, change in hemodynamic status, and obesity.

Other Biomarkers

There are several other biomarkers under investigation that may show promise in predicting CTRCD. Myeloperoxidase is an enzyme that is involved in lipid peroxidation and is typically released in periods of inflammatory, oxidative stress by neutrophils. Myeloperoxidase is being considered as a biomarker as it believes that oxidative stress is one of the mechanisms of doxorubicin and trastuzumab cardiotoxicity. It found in a study of 78 patients that a greater risk of cardiotoxicity (46.5%) correlated with patients with the most significant change in both troponin >0.121 ng/mL and MPO >422.6 pmol/L. It suggests that MPO can be an adjunct biomarker to troponin, although further studies are needed to confirm these findings.35 Other biomarkers receiving attention are growth differentiation factor 15 (GDF-15), Phosphatidylinositol-glycan biosynthesis class F protein (PIGF), soluble FMS-like tyrosine kinase receptor-1, and galectin 3. GDF-15 is a member of the transforming growth factor β (TGF-β) cytokine superfamily with increased expression during events of ischemia, mechanical stretch, and oxidative stress. PIGF is a member of the vascular endothelial growth factor family and is under investigation as it may reflect the direct action of anthracycline and trastuzumab on angiogenesis. Galectin-3 levels increase in patients with acute heart failure. None of these biomarkers were associated with increased risk of CTRCD, although these results may be due to small sample sizes [32,33]. In summary, different biomarkers have evaluated for the early diagnosis and prediction of CTRCD. Current studies have found a significant relation between the late and persistent elevation of troponin level and the development of cardiac toxicity after cancer therapy. However, there are still unanswered questions regarding the appropriate timing of the level measurements and its role in the surveillance during treatment using target therapies. However, the available evidence for other biomarkers is conflicting or has derived from small studies requiring additional investigation

Conclusions

Identification and treatment of subclinical LV dysfunction associated with cancer therapy are essential for improvement of cardiac outcomes. Dazzling progression in the cardiac field have caused scientific progress in the laboratory test, enhancement the availability of diagnostic tools in research and clinical practice. Current expert consensus recommends a comprehensive evaluation of the patient at risk of CTRCD; it includes the use of traditional and novel noninvasive imaging techniques as the preferred the diagnostic method, as well as an integrated approach combining biomarkers and imaging modalities for risk stratification and surveillance of cardiotoxicity in selected patients. Future prospective randomized controlled trials are required to determine the optimal diagnostic strategies using traditional and new biomarkers. These strategies should be individualized taking into account the patient's cardiovascular risk and the potential cardiotoxic effect of the therapy plan.

References

1. Miller KD, Siegel RL, Lin CC, Mariotto AB, Kramer JL, et al. Cancer treatment and survivorship statistics, 2016. CA Cancer J Clin. 2016; 66: 271–289.
2. Seidman A, Hudis C, Pierri MK, Shak S, Paton V, et al. Cardiac dysfunction in the trastuzumab clinical trials experience. J Clin Oncol. 2002; 20: 1215–1221.
3. Yeh ET, Bickford CL. Cardiovascular complications of cancer therapy: incidence, pathogenesis, diagnosis, and management. J Am Coll Cardiol. 2009; 53: 2231–2247.
4. Friedman MA, Bozdech MJ, Billingham, ME, Rider, AK. Doxorubicin cardiotoxicity. Serial endomyocardial biopsies and systolic time intervals. JAMA.1978; 240: 1603–1606.
5. 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: 185–229.

6. Swain SM, Whaley FS, Ewer MS. Congestive heart failure in patients treated with doxorubicin: a retrospective analysis of three trials. Cancer. 2003; 97: 2869–2879.

7. Slamon D, Eiermann W, Robert N, Pienkowski T, Martin M, et al. Adjuvant trastuzumab in HER2- positive breast cancer. N Engl J Med. 2011; 365: 1273–1283.

8. Plana JC, Galderisi M, Barac A, Ewer MS, Ky B, et al. Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: a report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2014; 27: 911–939.

9. Curigliano G, Cardinale D, Suter T, Plataniotis G, de Azambuja E, et al. Cardiovascular toxicity induced by chemotherapy, targeted agents and radiotherapy: ESMO Clinical Practice Guidelines. Ann Oncol. 2012; 23: 55–166.

10. Zamorano JL, Lancellotti P, Rodriguez-Munoz D, Aboyans V, Asteggiano R, et al. ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: the task force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC). Eur Heart J. 2016; 37: 2768–2801.

11. American College of Emergency Physicians; Society for Cardiovascular Angiography and Interventions, O'Gara PT, Ascheim DD, Casey DE Jr, Chung MK, de Lemos JA, et al. ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013; 61: e78–e140.

12. Lipshultz SE, Rifai N, Sallan SE, Lipsitz SR, Dalton V, et al. Predictive value of cardiac troponin T in pediatric patients at risk for myocardial injury. Circulation. 1997; 96: 2641–2648.

13. Lipshultz SE, Scully RE, Lipsitz SR, Sallan SE, Silverman LB, et al. Assessment of dexrazoxane as a cardioprotection in doxorubicin-treated children with high-risk acute lymphoblastic leukemia: long-term follow-up of a prospective, randomized, multicentre trial. Lancet Oncol. 2010; 11: 950–961.

14. Cardinale D, Colombo A, 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: 213–220.

15. Cardinale D, Sandri MT. The role of biomarkers in chemotherapy-induced cardiotoxicity. Prog Cardiovasc Dis. 2010; 53: 121–129.

16. Cardinale D, Sandri MT, Colombo A, Colombo N, Boeri M, et al. Prognostic value of troponin I in cardiac risk stratification of cancer patients undergoing high-dose chemotherapy. Circulation. 2004; 109: 2749–2754.

17. Cardinale D, Sandri MT, Martinoni A, Borghini E, Civelli M, et al. Myocardial injury revealed by plasma troponin I in breast cancer treated with high-dose chemotherapy. Ann Oncol. 2002; 13: 710–715.

18. Cardinale D, Colombo A, Torrisi R, Sandri MT, Civelli M, et al. Trastuzumab-induced cardiotoxicity: Clinical and prognostic implications of troponin I evaluation. J Clin Oncol. 2010; 28: 3910–3916.

19. Fallah-Rad N, Walker JR, 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: 2263–2270.

20. Tan-Chiu E, Yothers G, Romond E. Assessment of cardiac dysfunction in a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel, with or without trastuzumab as adjuvant therapy in node-positive, human epidermal growth factor receptor 2-overexpressing breast cancer: NSABP B-31. J Clin Oncol. 2005; 23: 7811–7819.

21. de Korte MA, de Vries EGE, Lub-de Hooge MN, Jager PL, Gietema JA, et al. 111Indium-trastuzumab visualizes myocardial human epidermal growth factor receptor two expressions shortly after anthracycline treatment but not during heart failure: a clue to uncover the mechanisms of trastuzumab-related cardiotoxicity. Eur J Cancer. 2007; 43: 2046–2051.

22. Bertsch T, Bleuel H, Aufenanger J, Rebel W. Comparison of cardiac Troponin T and cardiac Troponin I concentrations in peripheral blood during orciprenaline induced tachycardia in rats. Exp Toxicol Pathol. 1997; 49: 467–468.

23. Mair J, Artner-Dworzak E, Haid C, Wicke K, Judmaier K, et al. Cardiac troponin T in the diagnosis of acute myocardial infarction. Clin Chem. 1991; 37: 845–852.

24. Adamcova M, Lencova-Popelova O, Jirkovsky E, Simko F, Gersl V, et al. Experimental determination of diagnostic window of cardiac troponins in the development of chronic anthracycline cardiotoxicity and estimation of its predictive value. Int J Cardiol. 2015; 201: 358–367.

25. Pichon M-F, Cvitkovic F, Hacene K, Delaunay J, Lokiec F, et al. Drug-induced cardiotoxicity studied by longi-

tudinal B-type natriuretic peptide assays and radionuclide ventriculography. In Vivo. 2005; 19: 567–576.

26. Romano S, Fratini S, Ricevuto E, Procaccini V, Stifano G, et al. Serial measurements of NT-proBNP are predictive of not-high-dose anthracycline cardiotoxicity in breast cancer patients. Br J Cancer. 2011; 105: 1663–1668.

27. Sandri MT, Salvatici M, Cardinale D, Zorzino L, Passerini R, et al. N-terminal pro-B-type natriuretic peptide after high-dose chemotherapy: a marker predictive of cardiac dysfunction? Clin Chem. 2005; 51: 1405–1410.

28. Skovgaard D, Hasbak P, Kjaer A. BNP predicts chemotherapy-related cardiotoxicity and death: comparison with gated equilibrium radionuclide ventriculography. PLoS ONE. 2014; 9: 96736.

29. Sawaya H, Sebag IA, Plana JC, Januzzi JL, Ky B, et al. Early detection and prediction of cardiotoxicity in chemotherapy-treated patients. Am J Cardiol. 2011; 107: 1375–1380.

30. Hayakawa H, Komada Y, Hirayama M, Hori H, Ito M, et al. Plasma levels of natriuretic peptides about doxorubicin-induced cardiotoxicity and cardiac function in children with cancer. Med Pediatr Oncol. 2001; 37: 4–9.

31. Lipshultz SE, Landy DC, Lopez-Mitnik G, Hinkle AS, Constine LS, et al. Cardiovascular status of childhood cancer survivors exposed and unexposed to cardiotoxic therapy. J Clin Oncol. 2012; 30: 1050–1057.

32. Ky B, Putt M, Sawaya H, French B, Januzzi JL Jr, 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: 809–816.

33. van Boxtel W, Bulten BF, Mandigers CM, Joosten LA, Kapusta L, et al. New biomarkers for early detection of cardiotoxicity after treatment with docetaxel, doxorubicin, and cyclophosphamide. Biomarkers. 2015; 20: 143–148.