Early Detection of Myocardial Damage: A Multimodality Approach

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Abstract

Cardiovascular diseases are possible complications of antineoplastic treatment and may lead to premature morbidity and mortality among cancer survivors. A symptom-based follow-up is ineffective, and there are growing evidences that early detection of myocardial damage in patients treated with antineoplastic drugs is the key point to prevent the occurrence of damage and improve the prognosis of these patients. Different techniques have been proposed to monitor cardiac function in oncologic patients such as cardiac imaging (echocardiography, nuclear imaging, and cardiac magnetic resonance) and biomarkers (troponin and natriuretic peptides). The European Association of Cardiovascular Imaging/American Society of Echocardiography consensus document encourages an integrated approach to early detect cardiotoxicity.

Keywords: Cardiotoxicity, deformation imaging, early detection, echocardiography, multimodality approach

INTRODUCTION

In recent years, chemotherapy has significantly improved the overall prognosis and survival of several oncologic patients. However, a significant proportion of cancer survivors are living with long-term adverse effects of cancer therapy, involving multiple organ systems.1-3 Cardiovascular diseases are one of the most frequent of these side effects and may lead to premature morbidity and mortality among cancer survivors.1,4

For these reasons, there is a growing interest for early detection of myocardial damage in patients treated with antineoplastic drugs in order to readily intervene with cardioprotective strategies, allow the prosecution of antineoplastic treatment, and avoid the need of its discontinuation.

Nowadays, it remains unclear which approach would be best in order to prevent chemotherapy-induced cardiotoxicity (CTX).5,6 Main proposed strategies to monitor cardiac function in oncologic patients are cardiac imaging (echocardiography, nuclear imaging, cardiac magnetic resonance [CMR]) and biomarkers (troponin, natriuretic peptides). The choice of different modalities depends on local expertise and availability.1,3 Recent available data in the literature encourage the combination of multimodality imaging techniques as well as the use of biomarkers for early detection of cancer therapeutic-related cardiac dysfunction.6

CARDIOVASCULAR COMPLICATIONS OF ANTICANCER DRUGS

Antineoplastic treatments can induce cardiovascular damage that may appear early or, sometimes, many years after exposure.1,3 The majority of studies on CTX focus on patients treated with anthracyclines and trastuzumab. However, cardiotoxic effect has been described even for other classes of treatments such as tyrosine kinases inhibitors, antimetabolites, alkylating agents, taxanes, and radiotherapy.1,3 The most common adverse event is a reduction in left ventricular (LV) dysfunction that may progress to overt heart failure (HF); nevertheless, clinical manifestations of CTX are broad and can include arrhythmias, ischemia, valvular heart disease, pericardial disease, arterial and pulmonary hypertension, and thrombosis [Figure 1].

Left ventricular dysfunction and heart failure

LV dysfunction and HF are common and serious side effects of cancer treatment.1 A recent report from the American Society...
Coronary artery disease and peripheral artery disease
Myocardial ischemia is another side effect of several cancer therapies. The mechanisms by which these drugs cause myocardial ischemia are different and range from a direct vasospastic effect to endothelial injury and acute arterial thrombosis, to long-term changes in lipid metabolism, and consequent premature arteriosclerosis. Previous mediastinal radiotherapy may accelerate drug-related coronary damage.

Severe atherosclerotic and nonatherosclerotic peripheral artery disease in the lower extremities can occur in patients treated with inhibitors of tyrosine kinases or inhibitors of BCR-ABL kinase such as ponatinib.

Valvular and pericardial disease
Antineoplastic drugs do not directly affect cardiac valves, but valvular disease may be observed in patients with cancer for several reasons such as; radiotherapy that causes calcification and fibrosis of the aortic root, aortic cusps, mitral valve annulus, tips and commissures; and infective endocarditis due to pancytopenia associated to chemotherapy and secondary to LV dysfunction.

Acute pericarditis may occur with the use of anthracyclines, cyclophosphamide, cytarabine, and bleomycin, while chronic pericardial effusion is usually associated with radiotherapy.

Arterial hypertension
Arterial hypertension (AH) is a common side effect of several vascular endothelial growth factor inhibitors such as bevacizumab, sunitinib, and sorafenib. AH is an important cardiovascular risk factor and favor the occurrence of left ventricle dysfunction.

Arrhythmias
Arrhythmias can be present at baseline in 16%–36% of treated patients with cancer. In these patients, we can observe different kind of rhythm disturbs that range from ventricular arrhythmias secondary to QT prolongation, electrolyte disturbances, myocardial ischemia or ventricular dysfunction, to supraventricular arrhythmias, or conduction defects.

Thromboembolic events
Incidence of thromboembolic events in neoplastic patients is high and generally depend on cancer-related factors; however, some anticancer drugs such as thalidomide and cisplatin can have additional effects.

Pulmonary hypertension
Pulmonary hypertension is a rare, but serious complication of some cancer agents and stem cell bone marrow transplantation. Dasatinib can induce severe but often reversible precapillary pulmonary hypertension.

Recently, cyclophosphamide and other alkylating agents were suggested as contributing to the development of pulmonary hypertension in oncologic patients.

Echocardiography: from Conventional to Advanced Evaluation
Echocardiography is the most frequently used technique for routine monitoring of patients treated with antineoplastic treatments. Conventional evaluation provides the use of LVEF as reference parameter before and during chemotherapeutic treatments. Newer echocardiographic techniques, using three-dimensional (3D) technology or contrast echocardiography, have resulted in significant improvement in the accuracy of LVEF assessment. It was demonstrated that 3D-echocardiography was suitable and reproducible for assessing changes in LV volumes and LVEF compared with CMR and was capable to detect smaller changes in LVEF (~5%).

Contrast agents demonstrated an incremental value in the measurement of LV volume and LVEF when two or more
contiguous left ventricle endocardial segments are poorly visualized in apical views.[25,26] Contrast-enhanced images may provide larger volumes than unenhanced images that are more reproducible with those obtained with CMR.[27]

Unfortunately, decrease of LVEF is detectable when damage is considerable and possibility of recovery reduced, therefore, it is not suitable as an early indicator of CTX.[28,29] More advanced echocardiographic modalities, in particular, myocardial deformation imaging with speckle-tracking strain analysis, show great potential for detecting early myocardial damage in asymptomatic oncologic patients.[30-34] Global longitudinal strain (GLS) is very sensitive in identifying subtle loss of myocardial function.[35,36]

Recent studies demonstrated that reduction of GLS during chemotherapeutic treatments was predictive of CTX.[37,38] In particular, Sawaya et al.,[37] in a prospective study of 81 patients with breast cancer, observed that a longitudinal strain value less negative than 19% after the completion of anthracyclines was predictive of CTX. Diagnostic accuracy increased when cardiac troponin (cTn) was also measured. Negishi et al. demonstrated that an 11% reduction of GLS since baseline value is an independent early predictor of later reductions in EF, incremental to usual predictors in patients at risk for trastuzumab-induced CTX.[38] A recent study demonstrated that strain imaging is a powerful tool to identify an increased number of survivor with an early myocardial injury.[39] Therefore, measuring the percentage variation of GLS between follow-up and baseline seems to be an accurate approach to early detect CTX [Figure 2].

The European Society of Cardiology suggests that measurements of GLS during chemotherapy should ideally be compared with baseline value, and a relative percentage reduction of GLS of <15% from baseline is very likely to predict CTX.[1]

3D speckle-tracking echocardiography (STE) is a promising but not yet validated advanced techniques for the evaluation of myocardial function in the clinical practice. It was demonstrated that GLS evaluated by 3D-STE was superior to biomarkers and to LVEF in predicting future development of CTX.[40,41]

Measurement of diastolic function is recommended in cancer patients,[31] and frequently, it is impaired.[42] However, changes in loading conditions associated with chemotherapy (e.g., nausea, vomiting, and diarrhea) can affect E/e’ ratio, for these reasons the accuracy of this parameter in oncologic patients is still debated.

Finally, in cancer patients, stress echocardiography could be a further test that reveals the presence of subclinical LV dysfunction and coronary artery disease in patients with an intermediate or high pretest probability.[1,10]

In a recent study, Khouri et al.[43] observed that left ventricle contractile reserve, expressed as delta between resting and peak GLS, was significantly lower in patients receiving anthracycline for breast cancer than in the control group. Civelli et al.[44] demonstrated, in a population of adult women with breast cancer, the usefulness of echo stress with dobutamine in identifying subclinical LV dysfunction. In particular, the reduction in contractile reserve (reduction of FE ≥10% from baseline) has proved to be an important prognostic predictor.

**Cardiac Magnetic Resonance and Early Detection of Myocardial Damage**

The need for a reliable and accurate detection method for early cardiac damage has encouraged the introduction of the second-line advanced imaging modalities in oncologic patients, including CMR and CMR-based strain imaging.[45,46] CMR is the gold standard for quantifying biventricular volumes and ejection fraction. In the evaluation of CTX, the added value of CMR is represented by its capability for providing information on tissue characterization, such as edema, hyperemia, fibrosis, and iron overload.

Late gadolinium enhancement is commonly used as an imaging biomarker of discrete myocardial fibrosis in cardiomyopathies,[47] although its significance in CTX is uncertain.[48] Using T1 relaxometry-based approaches, commonly referred to as “T1 mapping,” it is possible to measure myocardial extracellular volume, which has been shown to
correlate with the degree of cardiac fibrosis. This technique should be a reliable and noninvasive method to detect early CTX, allowing serial monitoring of chemotherapy-induced CTX.

Finally, LV strain assessment by CMR may be a promising method to monitor subclinical myocardial dysfunction in cancer patients receiving chemotherapy.

Nowadays, CMR is recommended for the quantification of LVEF when the acoustic window is poor at echocardiogram or when we want to confirm the measurement of LVEF before withholding a treatment because of not wide availability and cost, unfortunately, it cannot be used routinely.

Radionuclide angiography (MUGA) was referred as the gold standard to evaluate left ventricle systolic function in patients undergoing chemotherapy for many years, but the main concern about its use regard radiation exposure. Actually, it is used as an adjunct and complementary technique to echocardiography.

**BIOMARKERS**

Cardiac biomarkers such as cTn and N-terminal-pro-brain natriuretic peptide (NT-proBNP) are molecular markers suggested to allow earlier detection of drug-induced CTX compared to LVEF measurement.

Tn is a serum biomarker of cardiac damage and its elevation in oncological patients has been shown to predict the future development of CTX. Cardinale et al. demonstrated that in patients with cancer treated with high doses of anthracyclines, the increase in cTn allows discrimination between patients with a low risk of developing chemotherapy-induced CTX and those at high risk, which require strict cardiac follow-up. Moreover, troponin elevation may guide an early treatment with cardioprotective treatment with enalapril, with relevant positive consequences on patients prognosis. It has been shown that in a population of patients with breast cancer, the combination of high-sensitivity troponin (hsTn) with GLS measurement might provide the greatest specificity (93% when both are altered) and sensitivity (87%, when one of two parameters is altered) to predict future CTX.

The role of BNP and NT-proBNP to detect subclinical cardiac damage is still under investigation and results of published studies are controversial. In particular, some studies demonstrated that BNP levels increase during anticancer therapy and correlated with impairment of diastolic and systolic function. However, in other studies, BNP was not predictive of EF change.

Inflammation biomarkers, such as C-reactive protein, cytokines, and parameters of oxidative stress, are under investigation, but their role in early detection of myocardial damage during chemotherapy is not yet established.

**MULTIMODALITY APPROACH: INCREMENTAL VALUE IN PREDICTING EARLY CARDIOTOXICITY**

There is increasing available data encouraging the combination of multimodality imaging parameters and techniques for early detection of cardiac dysfunction in oncologic patients. In particular, a combination of GLS and hsTn-I showed a better accuracy for the early identification of myocardial damage and was predictive of subsequent cardiac dysfunction in patients receiving trastuzumab after anthracyclines.

EACVI/ASE consensus document encourages an integrated approach to early detect CTX, particularly a strategy that include, in addition to LVEF assessment, the calculation of GLS and the measurement of troponin at baseline and during follow-up in order to compare changes during time is proposed.

**Table 1: Chronology in the occurrence of cardiac damage in patient undergoing antineoplastic treatment and possible prevention/treatment strategies**

| Time of exposure | Cardiac damage | Prevention/treatment strategies |
|------------------|----------------|--------------------------------|
| Baseline         | None           | Cardiovascular risk factors control and optimization of treatment of concomitant cardiac disease |
| Days/weeks       | Myocardial cell injury detectable by increase in cTn | Enalapril, Carvedilol |
| Months           | Cardiotoxicity with decrease in LVEF | ACE-I and BB |
| Years            | Cardiotoxicity with HF symptoms | ACE-I, BB, and diuretics |

cTn=Cardiac troponin, GLS=Global longitudinal strain, LVEF=Left ventricular ejection fraction, BB=Beta-blockers, HF=Heart failure, ACE-I=Angiotensin-converting enzyme-inhibitor

**Figure 3: Multimodality approach in the detection of cardiotoxicity**
However, further studies are needed for wider validation of this approach in the clinical setting.

Conclusions
Cardio-oncology is a newly emerging branch of cardiology with the aim of monitoring, early detection, prevention, and treatment of CTX related to oncologic treatments.

Early diagnosis of myocardial damage is crucial in this setting in order to avoid overt CTX and HF and to allow the prosecution of antineoplastic treatment.

Although, in recent years, research has made a lot of progress, it is necessary to identify and validate emerging techniques in a multimodal approach in order to increase our capability to early detect myocardial damage in oncologic patients.

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Conflicts of interest
There are no conflicts of interest.

References

1. Zamorano JL, Lancellotti P, Rodriguez Muñoz D, Aboyans V, Asteuggiano R, Galderisi M, et al. 2016 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;37:2768-801.

2. Plana JC, Galderisi M, Barac A, Ewer MS, Ky B, Scherrer-Crosbie M, et al. Multimodality imaging in cardio-oncology. J Oncol 2015;2015:263950.

3. Armen SH, Lacchetti C, Barac A, Carver J, Constine LS, Denduluri N, et al. Cardiovascular imaging. Eur Heart J Cardiovasc Imaging 2014;15:1063-93.

4. Hering D, Faber L, Horstkotte D. Echocardiographic features of radiation-associated valvular disease. Am J Cardiol 2003;92:226-30.

5. Hull MC, Morris CG, Pepine CJ, Mendenhall NP. Valvular dysfunction and carotid, subclavian, and coronary artery disease in survivors of Hodgkin lymphoma treated with radiation therapy. JAMA 2003;290:2831-7.

6. Brosius FC 3rd, Waller BF, Roberts WC. Radiation heart disease. Analysis of 16 young (aged 15 to 33 years) necropsy patients who received over 3,500 rads to the heart. Am J Med 1981;70:519-30.

7. Tamargo J, Caballero R, Delpon E. Cancer chemotherapy and cardiac arrhythmias: A review. Drug Saf 2015;38:129-52.

8. Khorana AA, Kuderer NM, Culakova E, Lyman GH, Francis CW. Development and validation of a predictive model for chemotherapy-associated thrombosis. Blood 2008;111:4902-7.

9. Seng S, Liu Z, Chiu SK, Proverbs-Singh T, Sonpavde G, Choueiri TK, et al. Risk of venous thromboembolism in patients with cancer treated with cisplatin: A systematic review and meta-analysis. J Clin Oncol 2012;30:4416-26.

10. Carrier M, Le Gal G, Tay J, Wu C, Lee AY. Rates of venous thromboembolism in multiple myeloma patients undergoing immunomodulatory therapy with thalidomide or lenalidomide: A systematic review and meta-analysis. J Thromb Haemost 2011;9:653-63.

11. Limsuwann A, Pakakasama S, Ruchanawutanon M, Hong-eng S. Pulmonary arterial hypertension after childhood cancer therapy and bone marrow transplantation. Cardiology 2006;105:188-94.

12. Montani D, Bergot E, Günther S, Savale L, Bergeron A, Bourdin A, et al. Pulmonary arterial hypertension in patients treated by dasatinib. Circulation 2012;125:2128-37.

13. Walker J, Bhullar N, Fallah-Rad N, Lytwyn M, Golian M, Fang T, et al. Role of three-dimensional echocardiography in breast cancer: Comparison with two-dimensional echocardiography, multiple-gated acquisition scans, and cardiac magnetic resonance imaging. J Clin Oncol 2010;28:3429-36.

14. Thavendiranathan P, Grant AD, Negishi T, Plana JC, Popovic ZB, Marwick TH. Reproducibility of echocardiographic techniques for sequential assessment of left ventricular ejection fraction and volumes: Application to patients undergoing cancer chemotherapy. J Am Coll Cardiol 2013;61:77-84.

15. Lang RM, Badano LP, Mor-Avi V, Alfaro J, Armstrong A, Erdogan L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: An update from the American society of echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2015;28:1-39.e14.

16. Mulvagh SL, Rakowski H, Vannan MA, Abdelmoneim SS, Becher H, Bierig SM, et al. Cardiovascular complications of cancer therapy: Incidence, pathogenesis, diagnosis, and management. J Am Coll Cardiol 2009;53:2231-47.

17. Artemian SH, Lacchetti C, Barac A, Carver J, Constine LS, Denduluri N, et al. Prevention and monitoring of cardiac dysfunction in survivors of adult cancers: American society of clinical oncology clinical practice guideline. J Clin Oncol 2017;35:893-911.

18. Pizzino F, Vizzari G, Qamar R, Bomzer C, Carerj S, Zito C, et al. Multimodality imaging in cardio-oncology. J Oncol 2015;2015:263950.

19. Plana JC, Galderisi M, Barac A, Ewer MS, Ky B, Scherrer-Crosbie M, 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. Eur Heart J Cardiovasc Imaging 2014;15:1063-93.

20. Herling D, Faber L, Horstkotte D. Echocardiographic features of radiation-associated valvular disease. Am J Cardiol 2003;92:226-30.
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2010;96:1137-41.
33. Bi X, Deng Y, Zeng F, Zhu Y, Wu Y, Zhao C, et al. Evaluation of epirubicin-induced cardiotoxicity by two-dimensional strain echocardiography in breast cancer patients. J Huazhong Univ Sci Technolog Med Sci 2009;29:391-4.
34. Ho E, Brown A, Barrett P, Morgan RB, King G, Kennedy MJ, et al. Subclinical anthracyle- and trastuzumab-induced cardiotoxicity in the long-term follow-up of asymptomatic breast cancer survivors: A speckle tracking echocardiographic study. Heart 2010;96:701-7.
35. Kang Y, Cheng L, Li L, Chen H, Sun M, Wei Z, et al. Early detection of anthracyle-induced cardiotoxicity using two-dimensional speckle tracking echocardiography. Cardio J 2013;20:592-9.
36. Stoodley PW, Richards DA, Hui R, Boyd A, Harnett PR, Meikle SR, et al. Two-dimensional myocardial strain imaging detects changes in left ventricular systolic function immediately after anthracyle chemotherapy. Eur J Echocardiogr 2011;12:945-52.
37. 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 anthracyles, taxanes, and trastuzumab. Circ Cardiovasc Imaging 2012;5:596-603.
38. Negishi K, Negishi T, Hare JL, Halaska BA, Plana JC, Marwick TH. Independent and incremental value of deformation indices for prediction of trastuzumab-induced cardiotoxicity. J Am Soc Echocardiogr 2013;26:493-8.
39. Corella Aznar EG, Ayerza Casas A, Jiménez Montañés L, Calvo Escribano MAC, Labarta Aizpun JI, Samper Villagrasa P, et al. Use of speckle tracking in the evaluation of late subclinical myocardial damage in survivors of childhood acute leukaemia. Int J Cardiovasc Imaging 2018;34:1373-81.
40. Mornoç, Manolis Af, Cozma D, Koureremos N, Zacharopoulou I, Ionaç A. The value of left ventricular global longitudinal strain assessed by three-dimensional strain imaging in the early detection of anthracylemediated cardiotoxicity. Hellenic J Cardio 2014;55:235-44.
41. Zhang KW, Finkelman BS, Gulati G, Narayan HK, Upshaw J, Narayan V, et al. Abnormalities in 3-dimensional left ventricular mechanics with anthracyle chemotherapy are associated with systolic and diastolic dysfunction. JACC Cardiovasc Imaging 2018;11:1059-68.
42. Di Lisi D, Bonura F, Maccione F, Peritore A, Meschisi M, Cuttitta F, et al. Chemotherapy-induced cardiotoxicity: Role of the tissue Doppler in the early diagnosis of left ventricular dysfunction. Anticancer Drugs 2011;22:468-72.
43. Khouri MG, Hornsby WE, Velazquez EJ, Jones LW, Douglas PS. Exercise stress testing with strain echocardiography is superior to resting echocardiography in identifying doxorubicin-induced preclinical LV dysfunction in breast cancer patients. Circulation 2011;124:Suppl 21 Abstract n.16399.
44. Civelli M, Cardinale D, Martorina A, Lamantia G, Colombo N, Colombo A, et al. Early reduction in left ventricular contractile reserve detected by dobutamine stress echo predicts high-dose chemotherapy-induced cardiotoxicity. Int J Cardiol 2006;111:120-6.
45. Pepe A, Pizzino F, Gargiulo P, Perrone-Filardi P, Cadeddu C, Mele D, et al. Cardiovascular imaging in the diagnosis and monitoring of cardiotoxicity: Cardiovascular magnetic resonance and nuclear cardiology. J Cardiovasc Med (Hagerstown) 2016;17 Suppl 1:S27-34.
46. Perazzolo Marra M, De Lazzari M, Zorzi A, Migliore F, Zilio F, Calore C, et al. Impact of the presence and amount of myocardial fibrosis by cardiac magnetic resonance on arrhythmical outcome and sudden cardiac death in nonischemic dilated cardiomyopathy. Heart Rhythm 2014;11:856-63.
47. Ylänén K, Poutanen T, Savikurki-Heikkilä P, Rinta-Kiikka I, Eerola A, Vettenranta K. Cardiac magnetic resonance imaging in the evaluation of the late effects of anthracyles among long-term survivors of childhood cancer. J Am Coll Cardiol 2013;61:1539-47.
48. Kammerlander AA, Marzullf BA, Zetter-Tufaro C, Aschauer S, Duca F, Bachmann A, et al. T1 mapping by CMR imaging: From historical validation to clinical implication. JACC Cardiovasc Imaging 2016;9:14-23.
49. Miller CA, Naish JH, Bishop P, Coutts G, Clark D, Zhao S, et al. Comprehensive validation of cardiovascular magnetic resonance techniques for the assessment of myocardial extracellular volume. Circ Cardiovasc Imaging 2013;6:373-83.
50. Skitch A, Mital S, Mertens L, Liu P, Kantor P, Grosse-Wortmann L, et al. Novel approaches to the prediction, diagnosis and treatment of cardiac late effects in survivors of childhood cancer: A multi-centre observational study. BMC Cancer 2017;17:519.
51. Hong YJ, Park HS, Park JK, Han K, Park CH, Kim TK, et al. Early detection and serial monitoring of anthracyle-induced cardiotoxicity using T1-mapping cardiac magnetic resonance imaging: An animal study. Sci Rep 2017;7:2663.
52. 60. Levis BE, Bankoff AE, Gietema JA, Burylo AM, Dorlo TP, van Hasselt JG, et al. Pharmacodynamic modeling of cardiac biomarkers in breast cancer patients treated with anthracyle and trastuzumab regimens. J Pharmacokinet Pharmacodyn 2018;45:431-42.
53. Novo G, Cadeddu C, Sucato V, Pignolo P, Romano S, Tocchetti CG, et al. Role of biomarkers in monitoring antibiotic cardiotoxicity. J Cardiovasc Med (Hagerstown) 2016;17 Suppl 1:S27-34.
54. Cardinale D, Sandri MT, Martorina A, Trica A, Civelli M, Lamantia G, et al. Left ventricular dysfunction predicted by early troponin I release after high-dose chemotherapy. J Am Coll Cardiol 2006;59:517-22.
55. 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;114:2474-81.
56. Levis BE, Bankoff AE, Shapiro CL. Cardiotoxic effects of anthracyle-based therapy: What is the evidence and what are the potential harms? Lancet Oncol 2017;18:e445-6.
57. Feola M, Gareno O, Oecelli M, Franchini A, Biggi A, Visconti G, et al. Cardiotoxicity after anthracyle chemotherapy in breast carcinoma: Effects on left ventricular ejection fraction, troponin I and brain natriuretic peptide. Int J Cardiol 2011;148:194-8.
58. Pistilliucci G, Cicora AA, Sciaccia V, Raponi M, Rossi R, Velti E, et al. Troponin I and B-type natriuretic peptide (BNP) as biomarkers for the prediction of cardiotoxicity in patients with breast cancer treated with adjuvant anthracyles and trastuzumab. Clin Ter 2015;166:e67-71.
59. Suzuki T, Hayashi D, Yamazaki T, Mizuno T, Kanda Y, Komuro I, et al. Late effects of anthracyle chemotherapy in breast carcinoma: What is the evidence and what are the potential harms? Lancet Oncol 2017;18:e445-6.
60. Feola M, Gareno O, Oecelli M, Franchini A, Biggi A, Visconti G, et al. Cardiotoxicity after anthracyle chemotherapy in breast carcinoma: Effects on left ventricular ejection fraction, troponin I and brain natriuretic peptide. Int J Cardiol 2011;148:194-8.
61. Feola M, Gareno O, Oecelli M, Franchini A, Biggi A, Visconti G, et al. Cardiotoxicity after anthracyle chemotherapy in breast carcinoma: Effects on left ventricular ejection fraction, troponin I and brain natriuretic peptide. Int J Cardiol 2011;148:194-8.
62. Piselliucci G, Cicora AA, Sciaccia V, Raponi M, Rossi R, Velti E, et al. Troponin I and B-type natriuretic peptide (BNP) as biomarkers for the prediction of cardiotoxicity in patients with breast cancer treated with adjuvant anthracyles and trastuzumab. Clin Ter 2015;166:e67-71.
63. Suzuki T, Hayashi D, Yamazaki T, Mizuno T, Kanda Y, Komuro I, et al. Late effects of anthracyle chemotherapy in breast carcinoma: What is the evidence and what are the potential harms? Lancet Oncol 2017;18:e445-6.
oxidoreductase 1 activity and increase of ROS production by NADPH oxidases are early biomarkers in doxorubicin cardiotoxicity. Biomarkers 2014;19:142-53.

67. Ky B, Putt M, Sawaya H, French B, Januzzi JL Jr., 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;63:809-16.

68. El Ghandour AH, El Sorady M, Azab S, El Rahman M. Human heart-type fatty acid-binding protein as an early diagnostic marker of doxorubicin cardiac toxicity. Hematol Rev 2009;1:29-32.

69. Horacek JM, Tichy M, Pudil R, Jebavy L. Glycogen phosphorylase BB could be a new circulating biomarker for detection of anthracycline cardiotoxicity. Ann Oncol 2008;19:1656-7.

70. Horie T, Ono K, Nishio H, Nagao K, Kinoshita M, Watanabe S, et al. Acute doxorubicin cardiotoxicity is associated with miR-146a-induced inhibition of the neuregulin-ErbB pathway. Cardiovasc Res 2010;87:656-64.

71. Yu AF, Ky B. Roadmap for biomarkers of cancer therapy cardiotoxicity. Heart 2016;102:425-30.

72. Putt M, Hahn VS, Januzzi JL, Sawaya H, Sebag Ia, Plana JC, et al. Longitudinal changes in multiple biomarkers are associated with cardiotoxicity in breast cancer patients treated with doxorubicin, taxanes, and trastuzumab. Clin Chem 2015;61:1164-72.