Physiopathology and diagnosis of cardiotoxicity in patients submitted to chemotherapy treatment

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Abstract

Cardiovascular diseases and neoplastic diseases are the two main causes of morbidity and mortality in the world. Treated cancer patients usually develop cardiac diseases late in life due to chemotherapy-induced heart damage. The type of damage caused to the heart depends on the type of agent used during cancer treatment. It is expectable to observe ventricular impairment in patients treated with anthracyclines, while pyrimidines and some signalling inhibitors may damage the coronary circulation. Several techniques can be used to help diagnose early cardiac affections, such as biomarkers and auxiliary diagnostic tests. The information obtained can help physicians adjust chemotherapy doses, thus avoiding unnecessary heart damage. Although there is not yet a broad offer of cardioprotective drugs specific to these cases, some pharmacological agents used in common cardiology can also be applied here, such as beta-blockers and angiotensinogen-converting enzyme inhibitors.

Introduction

The oldest description of cancer dates back to 3000 B.C. when ancient Egyptian physicians described breast tumours and their removal, along with the words *there is no treatment*.[1,2]

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More than 5000 years have passed and nowadays, with the progress made in medicine and research, the understanding gained on the physiopathology of the disease, allows us to find new approaches to fight it, both in prevention and treatment. Nevertheless, cancer is still one of the biggest causes of death, with tremendous incidence, mortality and mobility.[3,4]

In 2008, 2.45 million patients were treated for all types of cancer in the 27 European Union member countries (EU-27) alone, and 1.23 million perished from the disease. Similar rates are found in the United States of America (USA). Economically speaking, in 2009, in the EU-27, costs associated with cancer reached 126 billion euros, of which 43 billion are attributed to early death associated with loss of productivity. Similar rates are found in the USA, where 157 billion euros were spent on the disease, of which 97 billion were due to mortality costs.[5,6]

As mentioned before, the progress in medical research gives us new forms of treatment, which are currently widely used against cancer, such as chemotherapy. Dozens of chemotherapy-based treatments are available, differentiated by the type of cancer and targets treated. Generally, we can classify chemotherapy drugs into two main groups: cytostatic chemotherapy, such as anthracyclines, alkylating agents and pyrimidines; and signalling inhibitors, such as anti-human epidermal growth factor receptor 2 (HER2) and angiogenesis inhibitors.[7-10] One of the main disadvantages of using chemotherapy-based treatments is the systemic toxicity induced on non-targeted organs, such as the heart. Cardiotoxicity studies have described cancer treatments as a serious problem which is causing an increase in the morbidity and mortality rates.[11,12] Each type of chemotherapy treatment has different collateral effects on the heart, depending on the cellular structure that is affected. The major cardiovascular consequences are ischaemia, left ventricular dysfunction/failure, arrhythmias (by virtue of ionic imbalance), arterial hypertension, myocardial infarction, vascular spasms, endothelial dysfunction and pericardial effusion (Table 1). Usually, the kind of damage done to the organ can be classified as type I, if the damage is irreversible or type II, if it is reversible.[13-17]

Physiopathological mechanisms

Several mechanisms are described in literature about the possible ways in which cardiac tissue is affected. Although each individual chemotherapy agent may have specific side effects, we will focus on a generalised view of the agents' actions, since many protocol treatments may include a combination of more than one agent.

Cytostatic agents affect the cardiomyocytes through lipidic peroxidation and oxidative stress, compromising the synthesis of Deoxyribonucleic Acid (DNA), Ribonucleic Acid (RNA) and,

consequently, protein formation. Once protein formation is faulty, cell performance is also compromised. In the case of anthracyclines, for example, there is a degradation of the myofilaments originating a negative imbalance of the sarcometric proteins, such as titin, causing cardiac sarcopenia. Cytostatic agents also act on cardiac stem cells, destroying them and compromising the heart's capacity to recover from inflicted damage.[18,19]

Other pathological mechanisms described are: mitochondrial damage affecting cellular bioenergetics, disequilibrium of adrenergic activity (adenylyl cyclase) related to a downregulation of calcium homeostasis. Those states compromise the ability of actin to bind with myosin, resulting in an ineffective contraction. Ionic balance is the central key in preventing malignant arrhythmias. If the concentration of intra an extracellular ions changes, the action potential responsible for the cell's depolarization will also change allowing for the development of arrhythmias, such as *torsades*.[14,20]

Signalling inhibitors, such as trastuzumab, act on HER2 which is overexpressed in some aggressive types of breast cancer, but also plays an important role in the survival and development of cardiomyocytes. The increase in angiotensin II is another side effect of this type of chemotherapy, leading to neuroregulin inhibition and the production of oxygen free radicals.[10,11,14,20]

The coronary arteries supply oxygenated blood to the heart. Changes in the normal blood flow in these vessels may have serious consequences on the general functioning of the organ. Before beginning chemotherapy, it is important to identify the presence (or not) of atherosclerotic plaques and, if present, follow their evolution during treatment. The vascular lesions mechanisms associated with signalling inhibitors are still unclear. VEGF stimulates the endothelium towards proliferation and survival, protecting the inner vascular layers and preventing the atherosclerotic process from taking place. Regarding the use of anti-VEGF agents, the regenerative properties of vascular endothelial cells will decrease leading to dysfunction and exposure of collagen fibres increasing the risk of thrombosis. Furthermore, anti-VEGF agents are also responsible for reducing nitric oxide and for increasing blood viscosity, exacerbating the possibility of a thrombotic event.[7,11]

Non-invasive diagnosis

Biomarkers for cardiac damage

Biomarkers are already commonly used to help physicians diagnose or classify the degree of heart disease, such as myocardial infarction or left ventricular dysfunction.[21]

Amongst them, troponin possesses one of the best sensitivity parameters for cardiac damage. When studied in relation to chemotherapy treatments, it reveals its peak after around 23 days of anthracycline administration.[22]

Despite the existence of two main types of troponins (I and T), it is the T-type that is commonly used in the diagnosis of left ventricular damage. This biomarker has an important, sensitive role when large doses of anthracyclines are employed, but lower doses must also be carefully interpreted.[22,23]

Natriuretic peptides are also commonly used when a suspicion of heart failure is listed on the patient's chart. As with troponin, there are also two main types, Atrial natriuretic peptide and Brain natriuretic peptide, the latter being more sensitive to changes in the ventricular chambers of the heart. Its increase is also associated with long QT intervals, responsible for the development of arrhythmias.[23-26]

Other biomarkers have been described, but are not commonly known nor have they been studied, such as, high-sensitive C-reactive protein used in trastuzumab-based treatments, glycogen phosphorylase BB, myeloperoxidase protein produced by the neutrophils leading to the release of oxygen free radicals, total anti-oxidant status used in leukaemia cases, neopterin and von Willebrand factor.[21-28]

In the past, some attention has been given to microRNAs, which are small non-coding RNA fragments whose function is to inhibit translation. They are found in almost every organ, as well as in the blood. Their presence or absence may indicate a pathological condition, depending on the type. MicroRNA-1, 17, 21, 44, 126, 133, 195, 199, 208 and 499 have shown to have some effect on the structure of the heart, and, because of that, they can be used in diagnosis. The problem is the time of expression once the organ has been damaged. This method is promising, but more studies and investigations are still needed.[10,29]

Auxiliary diagnostic tests

Other complementary methods are available to help diagnose cardiac dysfunction caused by chemotherapy agents.

Regardless of the fact that the examinations described below are commonly used in cardiology and not exclusive to the onco-cardiology specialty, they still provide helpful information with regard to cardiac status and should be used to optimize treatment dosages.

Electrocardiogram

The electrocardiogram (ECG) records the electric depolarization and repolarization action potentials of the heart. Electrolyte imbalance is frequent in treated cancer patients, making the occur-

Table 1. Most common chemotherapy agents and cardiac effect.

Chemotherapy agents			Cardiac damage
Cytostatic agents	Anthracyclines	Doxorubicin Daunorubicin Epirubicin Mitoxantrone	Ventricular dysfunction/Heart failure
	Alkylating agents	Cisplatin	Thrombosis
	Pyrimidine Analogues	Flurouracil Capecitabine	Coronary spasm/Ischaemia
Signalling inhibitors	Anti-HER2	Trastuzumab	Ventricular dysfunction
	Anti-VEGF	Sunitinib	Endovascular injury
		Bevacizumab	Hypertension/Contractile dysfunction

VEGF, vascular endothelial growth factor. Adapted from Sutter *et al*., 2013.[16]

rence of arrhythmias highly probable, as mentioned before. The ECG may show alterations that can be indicative and premonitory of these occurrences. The patterns typically associated are: long QT interval, premature supraventricular or ventricular contractions, atrial fibrillation, *torsade de pointes*, atrioventricular block and right branch block. Patterns associated with myocardial ischaemia (ST elevation, inverted Q waves) must be confirmed, as promptly as possible, by means of other diagnostic tests, especially in patients with chest pain.[30,31]

Transthoracic echocardiogram

The echocardiogram uses ultrasound to create images of the heart, usually bi-dimensional and, more recently, tri-dimensional pictures. It also provides information on pressure, volume, velocity and movement of the chambers.

The most frequent alterations are: reduced left ventricular ejection fraction, increased wall thickness, increased isovolumetric relaxation time, pericarditis and valvular sclerosis.

Other recently associated techniques may provide useful information. Tissue Doppler imaging records myocardial velocity allowing the examiner a precise evaluation of the heart movements at a chosen point. This is particularly important when evaluating diastolic function, as impaired relaxation is often the first sign of cardiac affection. As with other techniques, the cardiac contraction used to register tissue Doppler velocities must be normal. In patients with irregular rhythms the values should be carefully interpreted.[31-33]

Computed tomography angiography

Computed tomography angiography (CTA) uses x-rays and computerized analysis to obtain 3D images of the coronary vasculature, once these are assembled. It is less time consuming, cost-effective and safer when compared with regular angiography. In the last decade, CTA has been replacing regular angiography as far as the diagnosis and characterization of coronary diseases are concerned, especially in low to intermediate risk patients.[34]

Common abnormal findings include calcification of the proximal right coronary, left anterior descending artery and left circumflex arteries, stenosis of previous atherosclerotic lesions and *de novo* diffuse plaques.[34,35]

Angiography

Angiography is an invasive procedure and, therefore, not routinely used. However, when performed, it can provide information on ventricular function, valvular function and coronary circulation status.[9,32,36]

Protective methods

Despite the existence of some methods which can have protective features, the first course of action must be to reduce dosages to the minimum effective dose or change the chemotherapy agent for another less cardio-damaging.

Dexrazoxane

Dexrazoxane is a cardioprotective agent that binds to iron ions preventing them from forming free radicals. It has a better effect on women and helps to reduce troponin T levels. It must be carefully administered, since it can decrease anthracycline efficacy.[3,14,37,38]

Angiotensinogen converting enzyme inhibitors therapy

The main purpose of this therapy is to lower the blood pressure, reducing cardiac workload. It is also an anti-oxidant and has proven effective in increasing contractility and interstitial fibrosis.[8,16,39]

β-blockers

Widely used in cardiology, they act on the sympathetic nervous system reducing the heart rate, helping to lower the blood pressure and limit arrhythmic episodes.[40]

Its anti-oxidant properties protect the heart of cancer treated patients, and, like angiotensinogen converting enzyme inhibitors, it has a double benefit effect.[10,17]

Conclusions

Cardiovascular diseases and neoplastic diseases are the two main causes of morbidity and mortality in the world. Cardiac diseases, normally degenerative, usually present themselves late in life. On the other hand, cancer does not follow that pattern and is, unfortunately, present in all age groups. Therefore, any condition that combines the two illnesses must be taken seriously.

Cardiotoxicity is one of onco-cardiology's main concerns. Adjusting dose therapy without compromising heart function is essential to maintain morbidity levels at a minimum and improve health-related quality of life.

References

1. Hajdu SI. A Note from history: landmarks in history of cancer, part 1. Cancer 2011;117:1097-102.
2. Hajdu SI. 2000 Years of chemotherapy of tumors. Cancer 2005;103:1097-102.
3. Yusuf S, Razeghi P, Yeh E. The diagnosis and management of cardiovascular disease in cancer patients. Curr Probl Cardiol 2008;33:163-96.
4. Malvezzi M, Bertuccio P, Levi F, et al. European cancer mortality predictions for the year 2014. Ann Oncol 2014;9:1-7.
5. Fernandez R, Leal J, Gray A, Sullivan R. Economic burden of cancer across the european union: a population-based cost analysis. Lancet Oncol 2013;14:1165-74.
6. Mozaffarian D. Heart disease and stroke statistics - 2015 update. Circulation 2015;131:29-32.
7. Yeh E, Bickford C. Cardiovascular complications of cancer therapy. J Am Coll Cardiol 2009;53:2231-47.
8. Hahn V, Lenihan D, Ky B. Cancer therapy - induced cardiotoxicity: basic mechanisms ans potential cardioprotective thera. pies. J Am Heart Assoc 2014;3:1-14.
9. Monsuez J, Charniot J, Vignat N, Artigou J. Cardiac side-effects of cancer chemotherapy. Int J Cardiol 2010;144:3-15.
10. Adão R, Keulenaer G, Moreira A, Silva C. Cardiotoxicidade associada à terapêutica oncológica: mecanismos fisiopatológicos e estratégias de prevenção. Rev Port Cardiol 2013;32:395-409.
11. Chu T. Cardiotoxicity associated with tyrosine kinase inhibitor sinitinib. Lancet 2007;370:2011-9.
12. Small H, Montezano A, Rios F, et al. Hypertension due to antiangiogenic cancer therapy with vascular endothelial growth factor inhibitors: understanding and managing a new syndrome. Can J Cardiol 2014;30:534-43.
13. Jang S. Cardiovascular toxicity after antiangiogenic therapy in

persons older than 65 years with advanced renal cell carcinoma. Cancer 2016;122:124-30.
14. El-Awady E, Moustafa Y, Elmatty D, Radwan A. Cisplatin-induced cardiotoxicity: mechanisms and cardioprotective strategies. Eur J Pharmacol 2011;650:335-41.
15. Khakoo A. Heart failure associated with sinitinib malate - a multitargeted receptor tyrosine kinase inhibitor. Cancer 2008;112:2500-8.
16. Suter T, Ewer M. Cancer drugs and the heart: importance and management. Eur Heart J 2013;34:1102-111.
17. Dalen VEC, Kremer LCM. Cardioprotective interventions for cancer patients receiving anthracyclines. Cochrane Database Syst Rev 2004;4:1-4.
18. Kalam K, Marwick T. Role of cardioprotective therapy for prevention of cardiotoxicity with chemotherapy: a systematic review and meta-analysis. Eur J Cancer 2013;49:2900-9.
19. Cameron A, Touyz R, Lang N. Vascular complications of cancer chemotherapy. Can J Cardiol 2016;32:852-62.
20. Cheng H, Force T. Why do kinase inhibitors cause cardiotoxicity and what can be done about it? Prog Cardiovasc Dis 2010;53:114-20.
21. Eschenhagen T, Force T, Ewer MS, et al. Cardiovascular side effects of cancer therapies: a position statement from the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail 2011;13:1-10.
22. Christenson E, James T, Agrawal V, Park B. Use of biomarkers for the assessment of chemotherapy-induced cardiac toxicity. Clin Biochem 2015;48:223-35.
23. Cardinale D, Sandri MT, Martinoni A, et al. Myocardial injury revealed by plasma troponin I in breast cancer treated with high-dose chemotherapy. Ann Oncol 2002;13:710-5.
24. Murukesh N, Dive C, Jayson G. Biomarkers of angiogenesis ans their role in the development of VEGF inhibitors. Br J Cancer 2010;102:8-18.
25. Kalábová H. Intima-media thickness, myocardial perfusion and laboratory risk factos of atherosclerosis in patients with breast cancer treated with anthracycline-based chemotherpy. Med Oncol 2011;28:1281-287.
26. Lee HS, Son CB, Shin SH, Kim YS. Clinical correlation between brain natriuretic peptide and anthracycline-induced cardiac toxicity. Cancer Res Treat Off J Korean Cancer Assoc 2008;40:121-6.
27. Kozak K. Cardiac blood biomarkers in patients receving thoracic (chemo)radiation. Lung Cancer 2008;62:351-5.
28. Fallah-Rad N, Walker JR, Wassef A, et al. The utility of cardiac biomarkers, tissue velocity and strain imaging, and cardiac magnetic resonance imaging in predicting early left centricular dysfunction in patients with human epidermal growth factor receptor II - positive breast cancer treated with adjuvant trastuzumab therapy. JACC 2010;57:2263-70.
29. Koutova L. The impact of standart chemotherapy on miRNA signature im plasma in AML patients. Leuk Res 2015;39:1389-95.
30. Elme A. Eletrocardiography changes during adjuvant breast cancer therapy: incidence and risk factors. Anticancer Res 2013;33:4933-9.
31. Pizzino F, Vizzari G, Bomzer CA. Diagnosis of chemotherapy.induced cardiotoxicity. Patient Cent Res Rev 2014;1:121-7.
32. Fass L. Imaging and cancer: a review. Mol Oncol 2008;2:115-52.
33. Sawaya H. Assessment of echocardiography and biomarkers for the extended prediction of cardiotoxicity in patients treated with anthracyclines, taxanes, and trastuzumab. Circ Cardiovasc Imaging 2012;5:596-603.
34. Rademaker J. Coronary artery disease after radiation therapy for Hodgkin's lymphoma: coronary ct angiography findings and calcium scores in nine asymptomatic patients. Am J Roentgenol 2008;191:32-7.
35. Kupeli S. Evaluation of coronary artery disease by computed tomography in patients treated for childhood Hodgkin's lymphoma. J Clin Oncol 2009;28:1025-30.
36. Heidenreich PA, Schnittger I, Strauss HW. Screening for coronary artery disease after mediastinal irradiation for Hodgkin's disease. J Clin Oncol 2007;26:43-9.
37. Bansal N, Amdani SM, Hutchins KK, Lipshultz SE. Cardiovascular disease in survivors of childhood cancer. Curr Opin Pediatr 2018;30:628-38.
38. Cvetkovic RS, Scott LJ. Dexrazoxane: a review of its use for cardioprotection during anthracycline chemotherapy. Drugs 2005;65:1005-24.
39. López-Sendón J, Swedberg K, McMurray J, et al. Expert consensus document on angiotensin converting enzyme inhibitors in cardiovascular disease: the task force on ACE-inhibitors of the european society of cardiology. Eur Heart J 2004;25:1454-70.
40. Guglin M, Aljayeh M, Saiyad S. Introducing a new entity: chemotherapy-induced arrhythmia. Europace 2009;11:1579-86.