https://doi.org/10.31925/farmacia.2021.6.5 **REVIEW**

CARDIOTOXICITY OF ANTICANCER THERAPIES: FOCUS ON THE ROLE OF THE CARDIO-ONCOLOGICAL TEAM. A PRACTICAL REVIEW

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Abstract

In the last decades there were important improvements in oncological therapies which increased the survival of patients. However, patients and doctors are confronted with the side effects of the oncological therapy especially at the level of cardio-vascular system. The occurrence of the deleterious effects depends on the class of chemotherapy used and on the history of cardiac risk factors of the patients. Anthracyclines have the highest dose dependent cardiac toxicity and induce acute or long-term heart failure but fluoropyrimidines, cytokines, checkpoint inhibitors can induce myocardial ischemia, arrhythmia, pericardial effusion, vasculitis. Patients should be monitored by a cardio-oncological team. The cardio-vascular protection may be achieved by treating oncological patients who present a high cardiac risk with angiotensin converting enzyme inhibitors (ACEI)/angiotensin receptor blockers (ARB), beta blockers, and statins. The oncologist must select the class of medication that offers the best risk-benefit ratio and must sometimes decide alongside the cardiologist to temporary stop chemotherapy.

Rezumat

Ultimele decade au înregistrat progrese importante ale tratamentelor oncologice care au dus la creșterea speranței de viață a pacienților. Pe de altă parte, doctorii și pacienții s-au confruntat cu efectele secundare ale tratamentelor, mai ales cele cardio-vasculare. Apariția efectelor secundare depinde de clasa de citostatice utilizate și de profilul de risc cardio-vascular al pacientului. Antraciclinele au cea mai mare toxicitate cardiacă dependentă de doză și pot induce insuficiență cardiacă acută sau cronică, dar și fluoroprimidinele, citokinele, inhibitorii *checkpoint* pot induce ischemie miocardică, aritmii, revărsat pericardic, vasculită. Pacienții trebuie monitorizați de o echipă cardio-oncologică. Protecția cardiacă la pacienții oncologici cu risc cardio-vascular crescut se poate realiza prin administrarea de inhibitori ai enzimei de conversie a angiotensinei (ACEI)/blocanți de receptori de angiotensină (ARB), beta-blocante, statine. Oncologul trebuie sa aleagă clasa de medicamente care oferă balanța risc-beneficiu cea mai favorabilă, iar împreună cu cardiologul trebuie uneori să ia decizia importantă de oprire temporară a chimioterapiei.

Keywords: words cardiotoxicity, anthracyclines, ACEI, ARB, chemotherapy, oncological therapy

Introduction

Cancer is an impressive cause of morbidity and mortality all around the world in all age groups. In 2019 cancer was the first or second cause of death in people less than 70 years old in 112 countries, and the third or fourth in other 23 countries, from 183 studied, according to the World Health Organization [30]. The mortality from cancer rises steeply in patients around age 70 - 74 [6]. However, since 1990 there is a sustained trend in the reduction of the overall mortality from cancer compared to the previous years due to the more active oncological treatment. For example, in the US the reduction in oncological overall mortality was 29% in 2017 [29]. At the same time, the increased survival of oncological patients unmasks the cardiovascular risks of cancer therapy. There are various cardiac side effects depending on the cytostatic drug used and on the previous cardio-vascular history of the patient. For instance, anthracycline therapy can induce acute cardiomyopathy and heart failure in less than 1% of patients, an early onset disease in 1.6 - 2.1% of patients, and a late-onset disease in 1.6 - 5% [8]. According to the European Guidelines [33], the most elevated incidence of myocardial dysfunction is noted for doxorubicin (2 - 48%) and cyclophosphamide (2 - 28%) treatment. In the last years many guidelines are dealing with the cardiac toxicity of the oncological drugs [3, 8, 9, 31, 33]

and their periodical renewal reflects the continuous evolution of our knowledge in this field.

Definition of cardiotoxicity induced by anticancer drugs

According to the European Guidelines of Cardio-oncology, oncological cardiotoxicity is defined as "direct effects of the cancer treatment on heart function and structure or may be due to accelerated development of cardiovascular disease especially in the presence of traditional risk factors" [33]. These deleterious effects include (a) myocardial dysfunction and heart failure (HF), (b) coronary artery disease, (c) valvular heart disease, (d) tachy- or brady-arrhythmia, (e) pericardial involvement, (f) arterial hypertension, (g) peripheral artery disease, (h) stroke, (i) thromboembolic disease and (j) pulmonary hypertension [33].

Mechanisms of the cardiotoxicity induced by the oncological drugs

All cytotoxic drugs can induce cardiotoxicity in different proportions by various mechanisms. The analysis of the CARDIOTOX registry [24] which included 865 oncological patients aged 54.7 ± 13.9 identified an overall cardiotoxicity of the cytostatic drugs in 37.5% patients. However, a severe form defined as symptomatic heart failure (HF) or asymptomatic left ventricular ejection fraction (LVEF) < 40% was identified in only 3.1% during the 24 months of follow-up. However, the mortality rate was 22.9 *per* 100 patients-years in the severe cardiotoxicity group *versus* 2.3 *per* 100 patients-years in the rest. Among the classes of drugs used in oncology (Table I), the most cardiotoxic are the antineoplastic antibiotics, especially doxorubicin.

Myocardial dysfunction. There are two types of myocardial dysfunction responsible for heart failure. Type I myocardial dysfunction is found in case of anthracycline exposure. Anthracyclines inhibit topo-isomerase 2B and consequently break DNA double-strand, lead to mitochondria dysfunction, oxidative stress, reactive oxygen species and lipid peroxidation which damage the cardiomyocyte membrane [22]. Oxidative stress has been shown as an important contributor to the physiopathology of heart failure [18]. There are irreversible morphological changes of the cardiomyocytes leading to HF which can occur at the beginning of the drug administration, but is dose-related, or may occur long after treatment discontinuation [12]. Cardiotoxicity type I can also occur in patients treated with mitoxantrone, a topoisomerase 2 inhibitor indicated in metastatic hormone-dependent prostate cancer [22].

Table I

Heart failure in patients under anthracyclines and inhibitors of human epidermal growth factor receptor 2

Drug	Heart failure		
		Acute	Chronic
Antracyclines (cumulative doses)	Type I irreversible	1% During treatment	4 - 10% 1 to 7 years after the completion of treatment
Trastuzumab, pertuzumab, trastuzumab-emtansine, lapatinibe, (non-cumulative doses)	Type II reversible	7 - 34% (if with or preceded by anthracyclines) During treatment	

Type II myocardial dysfunction occurs under trastuzumab therapy, does not involve an anatomical damage of the cardiomyocytes, and is spontaneously reversible or disappears 2 - 4 months after the end of therapy. Trastuzumab binds to the extracellular domain of the human epidermal growth factor receptor 2 protein (HER-2), blocks the ErbB2 signalling pathway, and removes its protective effects on the sarcomere stability which maintains normal cardiac contractility [12, 22]. The concomitant administration of anthracyclines and trastuzumab increases the toxicity of anthracyclines. Type II cardiac toxicity can be induced also by other targeted drugs such as lapatinib, pertuzumab, imatinib, sorafenib, sunitinib, bevacizumab and bortezomib [22]. There are also other mechanisms involved in myocardial dysfunction, like haemorrhagic myonecrosis induced by high dose cyclophosphamide or coronary artery spasm induced by capecitabine [33]. Androgen deprivation therapy used in hormone-sensitive metastatic prostate cancer can induce subclinical cardiac dysfunction proved by changes in speckle tracking echocardiographic parameters, but with unknown precise mechanisms [15].

Coronary and peripheral artery disease. Cytotoxic drugs can damage the arterial wall and induce ischemia by many mechanisms: vasospasm by alterations in molecular signalling pathways that control vascular smooth muscle cell tone as induced by 5-fluorouracil, capecitabine, paclitaxel, docetaxcel; endothelial damage, enhanced thromboxane production, platelet activation and aggregation inducing vascular thrombosis in many vascular territories, as produced by cisplatin; endothelial apoptosis as induced by vinblastine; myonecrosis, vaso-spasm and Prinzmetal angina, as induced by cyclo-phosphamide; microvascular damage, rarefaction of the micro-vessels, interference with plaque neo-vessel formation, increased endothelin1 expression, reduced coronary functional reserve, as induced by vascular endothelial growth factors (VEGF) signalling pathway inhibitors like sunitinib; atherosclerotic plaque rupture, atherosclerotic vascular progression [17]. There are 2 types of vascular toxicity induced

by chemotherapy. Type I is a progressive alteration of vascular function after drug discontinuation and can occur in patients treated with tyrosine kinase inhibitors, like nilotinib and ponatinib. Type II of vascular toxicity disappears after the discontinuation of chemotherapy. 5-fluoro-uracil is an example of a drug that can induce type II vascular toxicity [12].

Arrhythmias. Cytostatic drugs can induce ventricular arrhythmias, the most dangerous being ventricular tachycardia type torsade de points (TdP). The mechanism of occurrence of TdP is the disturbance of the de-polarization/repolarization process in the cardiac cells which provokes the prolongation of the Q-T interval on ECG. Among cytostatic drugs, arsenic dioxide and tyrosine kinase inhibitor drugs, especially vandetanib, are most commonly involved in Q-T interval prolongation on ECG. The mechanism of Q-T interval prolongation induced by arsenic dioxide is the inhibition of cell membrane potassium channel and the mechanism of Q-T interval prolongation induced by tyrosine kinase inhibitors are enhanced by late sodium current and decreased potassium membrane currents [23]. The mechanism of Q-T interval prolongation induced by ribociclib is unknown. Prolongation of Q-T interval due to blocked potassium membrane channel can occur also in patients under androgen deprivation therapy for metastatic prostate cancer [14].

There are also other mechanisms of ventricular tachycardia without Q-T interval prolongation: myocardial ischemia secondary to coronary vasospasm (5-fluorouracil, capecitabine), myocardial inflammation (pembrolizumab), myocardial accumulation of reactive oxygen species (anthracyclines), or unknown mechanism for ventricular tachycardia induced by ibrutinib [23]. Other types of arrhythmias that can occur under chemotherapy are supraventricular tachycardia and atrial fibrillation, produced by various mechanisms: myocardial inflammation (pembrolizumab, CAR-therapy), direct myocardial irritation (cisplatin), phosphatidylinositol-3-kinase (PI3k) pathway inhibition (ibrutinib, sorafenib, vandetanib). Paclitaxel can induce bradycardia by acting on histamine receptor, and the tyrosine kinase inhibitor crizotinib induces bradycardia by decreasing funny current (i_f) in sinoatrial nodal cells [23].

Thromboembolic complications. Many cancers develop a prothrombotic state which can be accentuated by anthracycline, taxane, cisplatin, VEGF inhibitors [33]. Most patients experience venous thrombosis and some of them arterial thrombosis, with a worse prognosis.

Oncological patients under chemotherapy can also develop pericardial involvement, arterial hypertension, pulmonary embolism, infective, or marantic endocarditis. For instance, anthracyclines, cyclophosphamide, cytarabine and bleomycin can induce acute pericarditis [33]; tyrosine kinase inhibitors provoke arterial hypertension because of the induction of endothelial dysfunction (Table II) [28, 31].

Table II

Risk score of cardiotoxicity in oncological patients under chemotherapy

Oncological drugs		Patients risk factor		Risk calculation
Risk score 4	Anthracyclines, cyclophosphamide, ifosfamide, clofarabine, trastuzumab	1 point for each patient risk factor	Cardiomyopathy Arterial hypertension Heart failure Diabetes mellitus Age < 15 or > 65 years Female gender Prior or concomitant administration of anthracyclines	Risk score related to oncological drugs + 1 point for each patients risk factor > 6: very high 5 - 6: high 3 - 4: intermediate 1 - 2: low 0: very low
Risk score 2	Docetaxel, pertuzumab, sunitinib, sorafinib,			
Risk score 1	Bevacizumab, dasatinib, imatinib, lapatinib			
Risk score 0	Etoposide, rituximab, thalidomide			

Radiotherapy associated with cytostatic therapy increases the lifelong risk of occurrence of cardiotoxicity, by causing inflammation and subsequent fibrosis [33].

Class-specific cardiotoxicity

Anthracyclines and inhibitors of human epidermal growth factor receptor 2 (HER2), either antibodies (trastuzumab, pertuzumab, trastuzumab-emtansine) or tyrosine kinase inhibitors (lapatinib) can induce cardiac dysfunction, heart failure (Table I).

Cyclophosphamide, ifosfamide, cisplatin, paclitaxel, docetaxel can induce HF occurring during chemotherapy especially in multiple drug association or high doses. They can also induce cardiac ischemia, atrial fibrillation, bradycardia, pericardial effusion, pulmonary hypertension (cyclophosphamide).

5-FU, cisplatin bevacizumab, nilotinib, erlotinib, checkpoint inhibitors can provoke venous thromboembolic disease.

Checkpoint inhibitors (nivolumab, pembrolizumab, durvalumab, atezolizumab, avelumab, ipilimumab), can cause myocarditis, acute heart failure, arrhythmia, tachycardia, pericardial effusion, vasculitis.

B specific T-cell engager (blinatumomab) can induce tachycardia, hypotension and fatal heart failure.

The cardiotoxicity of paclitaxel and docetaxel is below that of anthracyclines [22].

Cytokines (interferon alfa-aldesleukin) can induce myocardial infarction, myocarditis, cardiac arrest, hypotension and tachycardia [34].

CAR-Tcell (tisagenlecleucel, axicabtagene, cilocleucel) can induce tachycardia, arrhythmia, cardiac arrest, hypotension, cardiogenic shock.

Fluoropyrimidines (5-FU, capecitabine, gemcitabine), etoposide, bevacizumab, bleomycin, sorafenib, sunitinib can induce cardiac ischemia, atrial fibrillation, bradycardia. Up to 18% patients under fluoropyrimidines develop manifest myocardial ischemia and up to 10% silent myocardial ischemia [33].

Aromatase inhibitors are associated with an increased risk of heart failure and cardiovascular mortality.

Methods of evaluation of the cardiotoxicity

History of cardiovascular disease and clinical evaluation are invaluable for the assessment of the cardiovascular risk under oncological treatment

The assessment on ECG of the various pathological changes and the measurement of Q-T interval corrected to the heart rate with Friedericia or Bazett formula are very important (Q-Tc). The maximal normal length of Q-Tc is 460 ms in women and 440 ms in men. According to guidelines, a Q-Tc >500 ms or an increase of > 60 ms comparing to the basely e value are pathological [33].

Echocardiography. The occurrence of HF under chemotherapy is defined by the > 10% reduction from the baseline of left ventricular ejection fraction (LVEF) to a value of 53%, considered the lower limit of the normal, evaluated by 2D or 3D echocardiography [13, 33]. However, according to ESMO Practice Guidelines [9], cardiotoxicity is considered at a decrease of LVEF by 5% or more to less than 55% in the presence of symptoms of HF or an asymptomatic decrease in EF by 10% or more to less than 55%. A reduction of > 15% from the baseline of global longitudinal strain (GLS) evaluated by speckle tracking technique is a sign of cardiotoxicity. According to SUCCOUR study recent data, GLS evaluation is more sensitive than LVEF for the detection of early myocardial dysfunction under cytostatic drugs [26].

Nuclear cardiac images like multigated radionuclide angiography (MUGA), 99mTC gated blood-pool single-photon emission computed tomography (SPECT), and *cardiac magnetic resonance imaging (MRI)* are not currently recommended in patients under oncological treatments. However, a > 10% decrease in LVEF with a value < 50% by nuclear cardiac images are markers of cardiac toxicity [10, 27, 33].

Biomarkers, N-terminal pro-B type natriuretic peptide (NT-proBNP), high sensitivity cardiac troponin (hs-cTn) are not included for now in the algorithm of evaluation of oncological cardiotoxicity, but considering some data these biomarkers' fluctuations can reveal subtle early changes [26]. There are also other biomarkers like microRNA, myeloperoxidase, markers of extracellular matrix turnover, which are investigated for more specific and early evidence of both acute and chronic oncological cardiotoxicity [4].

Risk factors for cardiac toxicity in oncological patients under chemotherapy

The cardiac toxicity of the cytostatic drugs depends on the risk profile of the patients and on the class of the drugs used.

The risk profile of the patients. The risk of cardiotoxicity of the cytostatic drugs is more elevated in women, patients aged under 15 or over 65 years, with more than two risk factors: arterial hypertension with values more than 140/90 mmHg (160/90 mmHg if over 80 years old), diabetes mellitus with HbA1c more than 7.5%, dyslipidaemia, smoking, obesity (body mass index more than 25 kg/m^2), sedentary lifestyle (less than 2.5 hours/week moderate to intense physical activity), thyroid dysfunction, electrolyte abnormalities, stage ≥ 2 chronic kidney disease, history of heart disease (heart failure, cardiomyopathies, borderline LVEF between 50 - 59%, atrial fibrillation, supraventricular tachycardia, prolonged Q-T interval, ventricular tachycardia), moderate to severe valvular heart disease [31]; elevated baseline or during cancer therapy of troponin and/or NTproBNP [11].

The risk profile of the treatment. The risk of cardiotoxicity is increased in patients receiving high dose anthracyclines (≥ 250 mg/m^2 doxorubicin or ≥ 600 mg/m^2 epirubicin), lower doses of anthracyclines, or HER inhibitors, or VEGF inhibitors, or proteasome inhibitors or Bcr-Abl inhibitors associated with ≥ 2 previous risk factors of the patients; lower doses of anthracycline associated with trastuzumab or radiotherapy; a dose of thoracic radiotherapy more than 30 Gy [3, 31].

A risk score for oncological cardiotoxicity was proposed considering the oncological medication administrated and the medical history of the patient [22] (Table II).

Monitoring and management recommendations take into account the risk score of the patient [22] (Table III).

Table III

Indication of monitoring of oncological patients under chemotherapy

Risk score	Methods	Monitoring	Principles of management
> 6	ECG (Q-Tc) TTE (LVEF, GLS) hs-cTn	Before every cycle of oncological treatment, at the end of the treatment, 3-6 months later, 1 year after the completion of the treatment	ACEI, ARB, beta-blockers (carvedilol), statins initiated a week before the oncological treatment and continued thereafter
5 - 6		Every 3 cycles of treatment, at the end of the treatment, 3-6 months and 1 year after the completion of the treatment	Initiate ACEI/ARB, beta-blockers (carvedilol) and/or statin

Risk score	Methods	Monitoring	Principles of management
3 - 4		Mid-term and end of the treatment, 3-6 months after the completion of chemotherapy	Discuss risks and benefits of the therapy
1 - 2		Optional, at the end of the chemotherapy	None
0		None	None

ACEI = angiotensin converting enzyme inhibitors; ARB = angiotensin 2 receptor blockers; TTE = transthoracic echocardiography; LVEF = left ventricular ejection fraction; hs-cTn = high sensitivity cardiac troponin; GLS = global longitudinal strain

Cardiotoxicity prevention

Preventing cardiotoxicity of oncological drugs involves several steps: recognizing the cardiovascular risks, considering all the risk factors, choosing the oncological treatment according to the risk factors of the patient, monitoring the state of the cardiovascular system during the treatment and thereafter [25].

The correct evaluation of the patients regarding the cardiovascular history and the treatment of the concurrent cardiovascular diseases or risk factors are the most important facts protecting the heart from the deleterious effects of oncological therapies.

Patients with concurrent cardiovascular problems must be treated and undergo periodical clinical, ECG, TTE and hs-cTn evaluation. Angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB), statins, beta-blockers must be initiated before the oncological therapy if the risk score is very high or at the moment of oncological therapy if the risk score is high [4]. However, the results of the studies regarding the protective effects of beta-blockers in patients under chemotherapy are controversial. CECCY study [5] demonstrated the favourable effects of carvedilol on the hs-cTn and diastolic function of the heart, but no influence on LVEF in 300 Brazilian patients with HER-2 negative breast cancer treated with anthracycline, cyclophosphamide, and taxane. PRADA study [16] included 130 women with early breast cancer and no cardiac problems and received angiotensin receptor blocker candesartan cilexetil, or beta-blocker metoprolol succinate, or both, or matching placebo concomitant with adjuvant anticancer therapy. Candesartan, but not metoprolol had prevented the decrease of LVEF. Acar *et al.* [2] demonstrated in 40 patients under anthracyclines that atorvastatin 40 mg o.d. prevents the decrease of LVEF. Husam Abdel-Qadi *et al*. [1] demonstrated in 666 patients with breast cancer under anthracycline and 390 patients under trastuzumab that concomitant treatment with a statin reduced the risk of HF hospitalization in anthracycline, but not in the trastuzumab group. Cardinale *et al*. [7] studied 473 patients under chemotherapy who received or not enalapril 20 mg o.d. They demonstrated that early treatment with enalapril prevents the development of late cardiotoxicity evaluated by increased TnI. Nevertheless, according to another study [13] enalapril did not prevent LVEF decline when administered during chemotherapy.

Cardiac therapy is optional in patients with intermediate score risk and it is not indicated in patients with low score risk. Kong *et al*. [20] performed a systematic review of published literature which included 30 randomized trials regarding the cardioprotective effects of beta-blockers, ACEI/ARB, statin, dexrazoxane in breast cancer patients. They found that in patients without a history of heart disease, these cardioprotective agents confer only marginal protection against LVEF decline.

Dexrazoxane belongs to the bis-dioxopiperazine compounds and is a water-soluble ring closed analogue of the iron chelator ethylenediaminetetraacetic acid [10]. It forms a tight complex with the ATPase domain of topoisomerase 2 and prevents anthracyclines from binding to the topoisomerase 2β–DNA complex [32]. It is considered a cardioprotective agent against anthracycline-induced cardiac toxicity, but in 2011 the European Medicines Agency recommended to use this medication only in adult patients who have received > 300 mg/m^2 doxorubicin or > 540 mg/m^2 epirubicin because of the risk of secondary cancer. Furthermore, a meta-analysis [19] demonstrated that prophylactic treatment with dexrazoxane has not a better efficacy for reducing cardiotoxicity compared to beta-blocker, statin or ACEI/ARB.

Treatment of the cardiotoxicity which worsens during the chemotherapy is performed according to the cardiological guidelines. In patients with LVEF < 40% ESMO guidelines recommend cardioprotective therapy, first-line cancer therapy with cardio-oncology input and/or non-cardiotoxic second-line cancer treatment [9]. The same recommendations are cases of symptomatic HF, absolute LVEF decrease of > 20%. If there is an absolute LVEF decrease between 10% and 50% or persistent reduced LVEF, the guidelines recommend temporary cancer treatment withholding.

Conclusion

The cardiovascular risk of chemotherapy hinders the favourable results of the oncological treatment especially in elder patients with cardiac co-morbidities. These patients must be frequently monitored clinically, with ECG, echocardiography, cardiac biomarkers and treated according to the cardiovascular guidelines. The oncological-cardiological team must decide the continuation or withholding for the chemotherapy considering the risk/benefit balance of the patients.

Conflict of interest

The authors declare no conflict of interest.

References

1. Abdel-Qadir H, Bobrowski D, Zhou L, Austin PC, Calvillo-Argüelles O, Amir E, Lee DS, Thavendiranathan P, Statin Exposure and Risk of Heart Failure After Anthracycline- or Trastuzumab-Based Chemotherapy for Early Breast Cancer: A Propensity Score–Matched Cohort Study. *J Am Heart Assoc.*, 2021; 10(2): e018393: 1-18.
2. Acar Z, Kale A, Turgut M, Demircan S, Durna K, Demir S, Meriç M, Ağaç MT, Efficiency of atorvastatin in the protection of anthracycline-induced cardiomyopathy. *J Am Coll Cardiol.*, 2011; 58: 988-989.
3. Alexandre J, Cautela J, Ederhy S, Damaj GL, Salem JE, Barlesi F, Farnault L, Charbonnier A, Mirabel M, Champiat S, Cohen-Solal A, Cohen A, Dolladille C, Thuny F, Cardiovascular Toxicity Related to Cancer Treatment: A Pragmatic Approach to the American and European Cardio-Oncology Guidelines. *J Am Heart Assoc.*, 2020; 9(18): e018403: 1-33.
4. Ananthan K, Lyon AR, The Role of Biomarkers in Cardio-Oncology. *J Cardiovasc Transl Res.*, 2020; 13(3): 431-450.
5. Avila MS, Ayub-Ferreira SM, de Barros Wanderley MR Jr, das Dores Cruz F, Gonçalves Brandão SM, Rigaud VOC, Higuchi-Dos-Santos MH, Hajjar LA, Kalil Filho R, Hoff PM, Sahade M, Ferrari MSM, de Paula Costa RL, Mano MS, Bittencourt Viana Cruz CB, Abduch MC, Lofrano Alves MS, Guimaraes GV, Issa VS, Bittencourt MS, Bocchi EA, Carvedilol for Prevention of Chemotherapy-Related Cardiotoxicity: The CECCY Trial. *J Am Coll Cardiol.*, 2018; 71(20): 2281-2290.
6. Cancer mortality by age. Cancer Resarch UK, www.cancerresearchuk.org.
7. Cardinale D, Colombo A, Sandri MT, Lamantia G, Colombo N, Civelli M, Martinelli G, Veglia F, Fiorentini C, Cipolla CM, Prevention of high-dose chemotherapy-induced cardiotoxicity in high-risk patients by angiotensin-converting enzyme inhibition. *Circulation*, 2006; 114(23): 2474-2481.
8. Curigliano G, Cardinale D, Suter T, Plataniotis G, de Azambuja E, Sandri MT, Criscitiello C, Goldhirsch A, Cipolla C, Roila F; ESMO Guidelines Working Group, Cardiovascular toxicity induced by chemotherapy, targeted agents and radiotherapy: ESMO Clinical Practice Guidelines. *Ann Oncol.*, 2012; 23(Suppl 7): vii155-166.
9. Curigliano G, Lenihan D, Fradley M, Ganatra S, Barac A, Blaes A, Herrmann J, Porter C, Lyon AR, Lancellotti P, Patel A, DeCara J, Mitchell J, Harrison E, Moslehi J, Witteles R, Calabro MG, Orecchia R, de Azambuja E, Zamorano JL, Krone R, Iakobishvili Z, Carver J, Armenian S, Ky B, Cardinale D, Cipolla CM, Dent S, Jordan K; ESMO Guidelines Committee, Management of cardiac disease in cancer patients throughout oncological treatment: ESMO consensus recommendations. *Ann Oncol.*, 2020; 31(2): 171-190.
10. D'Amore C, Gargiulo P, Paolillo S, Pellegrino AM, Formisano T, Mariniello A, Della Ratta G, Iardino E, D'Amato M, La Mura L, Fabiani I, Fusco F, Perrone Filardi P, Nuclear imaging in detection and monitoring of cardiotoxicity. *World J Radiol.*, 2014; 6(7): 486-492.
11. Dobson R, Ghosh AK, Ky B, Marwick T, Stout M, Harkness A, Steeds R, Robinson S, Oxborough D, Adlam D, Stanway S, Rana B, Ingram T, Ring L, Rosen S, Plummer C, Manisty C, Harbinson M, Sharma V, Pearce K, Lyon AR, Augustine DX; British Society of Echocardiography (BSE) and the British Society of Cardio-Oncology (BCOS), BSE and BCOS Guideline for Transthoracic Echocardiographic Assessment of Adult Cancer Patients Receiving Anthracyclines and/or Trastuzumab. *JACC CardioOncol.*, 2021; 3(1): 1-16.
12. Ewer MS, Lippman SM, Type II chemotherapy-related cardiac dysfunction: time to recognize a new entity. *J Clin Oncol.*, 2005; 23(13): 2900-2902.
13. Georgakopoulos P, Roussou P, Matsakas E, Karavidas A, Anagnostopoulos N, Marinakis T, Galanopoulos A, Georgiakodis F, Zimeras S, Kyriakidis M, Ahimastos A, Cardioprotective effect of metoprolol and enalapril in doxorubicin-treated lymphoma patients: a prospective, parallel-group, randomized, controlled study with 36-month follow-up. *Am J Hematol.*, 2010; 85: 894-896.
14. Gheorghe ACD, Ciobanu A, Hodorogea AS, Radavoi GD, Jinga V, Nanea IT, Gheorghe GS, Evolution of Electrocardiographic Repolarization Parameters During Antiandrogen Therapy in Patients with Prostate Cancer and Hypogonadism. *Cardiovasc Toxicol.*, 2020; 20(4): 390-400.
15. Gheorghe ACD, Ciobanu A, Hodorogea AS, Radavoi GD, Jinga V, Rascu ASC, Nanea IT, Gheorghe GS, Subclinical left ventricular dysfunction in men under androgen deprivation therapy for prostate cancer, revealed by speckle-tracking-derived parameters, repolarization, and myocardial injury markers. *Echocardiography*, 2021; 38(4): 632-640.
16. Gulati G, Heck SL, Ree AH, Hoffmann P, Schulz-Menger J, Fagerland MW, Gravdehaug B, von Knobelsdorff-Brenkenhoff F, Bratland Å, Storås TH, Hagve TA, Røsjø H, Steine K, Geisler J, Omland T, Prevention of cardiac dysfunction during adjuvant breast cancer therapy (PRADA): a 2 × 2 factorial, randomized, placebo-controlled, double-blind clinical trial of candesartan and metoprolol. *Eur Heart J.*, 2016; 37(21): 1671-80.
17. Iliescu C, Grines CL, Herrmann J, Yang EH, Cilingiroglu M, Charitakis K, Hakeem A, Toutouzas K, Leesar MA, Marmagkiolis K, SCAI expert consensus statement: Evaluation, management, and special considerations of cardio-oncology patients in the cardiac catheterization laboratory (Endorsed by the Cardiological Society of India, and Sociedad Latino Americana de Cardiologıa Intervencionista). *Catheter Cardiovasc Interv.*, 2016; 87(5): 895-899.
18. Iliesiu A, Campeanu A, Marta D, Uscoiu G, Parvu I, Ciobanu A, Jinga M, Gheorghe G, Effects of high doses of allopurinol on serum uric acid and cardiac biomarkers in chronic heart failure. *Farmacia*, 2015; 63(4): 561-567.
19. Kalam K, Marwick TH, Role of cardioprotective therapy for prevention of cardiotoxicity with chemotherapy: a systematic review and meta-analysis. *Eur J Cancer.*, 2013; 49(13): 2900-2909.
20. Kong YC, Sener M, Subramaniam S, Bhoo-Pathy N, Role of cardioprotective therapies for prevention of cardiotoxicity in breast cancer: A systematic review

and meta-analysis. *Annals Oncology*, 2019; 30(Suppl9): ix140–ix150.
21. Langer SW, Dexrazoxane for the treatment of chemotherapy-related side effects. *Cancer Manag Res.*, 2014; 6: 357-363.
22. Larsen CM, Mulvagh SL, Cardio-oncology: what you need to know now for clinical practice and echocardiography. *Echo Res Pract.*, 2017; 4(1): R33-R41.
23. Lee DH, Chandrashekhar S, Fradley MG, Electrophysiologic Complications in Cancer Patients. *Methodist Debakey Cardiovasc J.*, 2019; 15(4): 282-288.
24. López-Sendón J, Álvarez-Ortega C, Zamora Auñon P, Buño Soto A, Lyon AR, Farmakis D, Cardinale D, Canales Albendea M, Feliu Batlle J, Rodríguez Rodríguez I, Rodríguez Fraga O, Albaladejo A, Mediavilla G, González-Juanatey JR, Martínez Monzonis A, Gómez Prieto P, González-Costello J, Serrano Antolín JM, Cadenas Chamorro R, López Fernández T, Classification, prevalence, and outcomes of anticancer therapy-induced cardiotoxicity: the CARDIOTOX registry. *Eur Heart J.*, 2020; 41(18): 1720-1729.
25. Mazilu L, Stănculeanu D-L, Gheorghe A-D, Voinea F, Suceveanu A-P, Pițuru S, Diaconu CC, Parepa I-R, Pantea Stoian A, Pop CS, Suceveanu A-I, Incidence of chemotherapy-induced peripheral neuropathy in cancer patients in clinical practice. *Farmacia*, 2019; 67(3): 472-476.
26. Negishi T, Thavendiranathan P, Negishi K, Marwick TH; SUCCOUR investigators, Rationale and Design of the Strain Surveillance of Chemotherapy for Improving Cardiovascular Outcomes: The SUCCOUR Trial. *JACC Cardiovasc Imaging.*, 2018; 11(8): 1098-1105.
27. Plana JC, Galderisi M, Barac A, Ewer MS, Ky B, Scherrer-Crosbie M, Ganame J, Sebag IA, Agler DA, Badano LP, Banchs J, Cardinale D, Carver J, Cerqueira M, DeCara JM, Edvardsen T, Flamm SD, Force T, Griffin BP, Jerusalem G, Liu JE, Magalhães A, Marwick T, Sanchez LY, Sicari R, Villarraga HR, Lancellotti P, 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(9): 911-939.
28. Shank Coviello J, Cardiovascular and Cancer Risk: The role of Cardio-oncology. *J Adv Pract Oncol.*, 2018, 9(2): 160-176.
29. Siegel RL, Miller KD, Fuchs HE, Jemal A, Cancer Statistics, 2021. *CA Cancer J Clin.*, 2021; 71(1): 7-33.
30. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F, Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.*, 2021; 71(3): 209-249.
31. Virizuela JA, Garcia AM, de las Penas R, Santaballa A, Andres R, Beato C, de la Cruz S, Gavila J, Gonzalez-Santiago S, Fernanedez TL, SEOM clinical guidelines on cardiovascular toxicity (2018). *Clin Transl Oncol.*, 2019; 21: 94-105.
32. Witteles RM, Bosch X, Myocardial Protection During Cardiotoxic Chemotherapy. *Circulation*, 2015; 132(19): 1835-1845.
33. Zamorano JL, Lancellotti P, Rodriguez Munoz D, Aboyans V, Asteggiano R, Galderisi M, Habib G, Lenihan DJ, Lip GY, Lyon AR, Lopez Fernandez T, Mohty D, Piepoli MF, Tamargo J, Torbicki A, Suter TM, ESC Scientific Document Group, 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(36): 2768-2801.
34. Zavalichi MA, Zavalichi SD, Statescu C, Arsenescu Georgescu MC, Cardiac pacing in acute right ventricular myocardial infarction. *RevMedChir.*, 2020; 124(4): 559-564.