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

GABRIELA SILVIA GHEORGHE 1,2, ANA CIOBANU 1,2*, ANDREEA SIMONA HODOROGEA 1,2, ANDREI CRISTIAN DAN GHEORGHE 1,2, RĂZVAN VALENTIN SCĂUNAȘU 1,2, IOAN TIBERIU NANEAA 1,2, MARINELA IONELA STOIAN 1,4, ADRIANA MIHAELA ILIESIU 1,2

1Faculty of Medicine, “Carol Davila” University of Medicine and Pharmacy, Bucharest, Romania
2Department of Internal Medicine and Cardiology, “Theodor Burghele” Clinical Hospital, Bucharest, Romania
3Department of General Surgery, Colțea Clinical Hospital, Bucharest, Romania
4Department of Cardiology, University and Emergency Hospital, 169 Splaiul Independenței, 050098, Bucharest, Romania

*corresponding author: ana.ciobanu@umfcd.ro

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 cardiovascular 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.

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 unmask the cardiovascular risks of cancer therapy. There are various cardiac side effects depending on the cytostatic drug used and on the previous cardiovascular 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].
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 topoisomerase 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].

| Heart failure in patients under anthracyclines and inhibitors of human epidermal growth factor receptor 2 |
|----------------------------------------------------------|
| **Drug** | **Acute** | **Chronic** |
|-----------|-----------|-------------|
| Antracyclines (cumulative doses) | Type I irreversible | 1% During treatment | 4 - 10% |
| Trastuzumab, pertuzumab, trastuzumab-emtansine, lapatinib, (non-cumulative doses) | Type II reversible | 7 - 34% (if with or preceded by anthracyclines) During treatment | 1 to 7 years after the completion of 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. Cytoxic 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, docetaxel; 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 depolarization/repolarization process in the cardiac cells which provokes the prolongation of the Q-T interval on ECG. Among cytostatic drugs, arsenic oxide 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 oxide is the inhibition of cell membrane potassium channel and the mechanism of Q-T interval prolongation induced by tyrosine kinase inhibitors is 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 ibritinib [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 (ibritinib, 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].

| Oncological drugs | Patients risk factor | Risk score related to oncological drugs + 1 point for each patients risk factor |
|-------------------|----------------------|--------------------------------------------------------------------------------|
| Risk score 4      | Anthracyclines, cyclophosphamide, ifosfamide, clofarabine, trastuzumab    | > 6: very high                                                                 |
| Risk score 2      | Docetaxel, pertuzumab, sunitinib, sorafenib, lapatinib                   | 5 - 6: high                                                                   |
| Risk score 1      | Bevacizumab, dasatinib, imatinib, lapatinib                             | 3 - 4: intermediate                                                           |
| Risk score 0      | Etoposide, rituximab, thalidomide                                        | 1 - 2: low                                                                    |
|                   |                       | 0: very low                                                                   |

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-entansine) 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).
CAR-T cell (tisagenlecleucel, axicabtagene,ciloleucel) 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, brady-cardia. 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 [9, 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/m²), 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/m² doxorubicin or ≥600 mg/m² epirubicin), lower doses of anthracyclines, or HER inhibitors, or VEGF inhibitors, or proteasome inhibitors or Bcr-Abi 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

| Risk score | Methods | Monitoring | Principles of management |
|------------|---------|------------|--------------------------|
| > 6        | ECG (Q-Tc), TTE (LVEF, GLS) | 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      | hs-cTn  | 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 |
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, 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 oncological therapy who received or not enalapril 20 mg o.d. They demonstrated that early treatment with enalapril prevents 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 thymidylate synthase 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/m² doxorubicin or > 540 mg/m² 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 chemotherapy 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.
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