Early diagnostics and prevention of anthracycline-induced cardiomyopathy – the role of cardiologist

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ABSTRACT

Anticancer antibiotics, anthracyclines, may cause severe left ventricle systolic dysfunction that is associated with poor clinical prognosis. In this review, we discuss the mechanisms and risk factors of anthracycline-induced cardiotoxicity and cardiomyopathy, among which the cumulative administered dose of anthracyclines and concurrent cardiovascular diseases are the most important. We also present strategies for primary and secondary prevention of anthracycline-induced cardiotoxicity via rigorous assessment of early signs of left ventricular dysfunction.

KEY WORDS: anthracycline-induced cardiomyopathy, doxorubicin, ejection fraction, prevention

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INTRODUCTION

The cardiotoxicity of anticancer medications has become a problem of utmost clinical importance. The survival of cancer patients has increased significantly over the past years, which has raised the rate of the delayed cardiotoxic effects of anti-tumor treatment [1]. Patients who have overcome cancer have an increased incidence of cardiovascular complications than their coevals [2]. Cardiotoxic effects of anti-tumor medications lead to the reduction of cumulative anthracycline doses, which may cause tumor under-treatment and poor outcome. Careful cardiologic assessment becomes a cornerstone of optimal management of such patients and should cover risk evaluation of cardiotoxic effects of anticancer drugs, the development of the individualized follow-up programs during and after chemotherapy, and the prevention and management of cancer treatment-induced cardiac dysfunction.

Almost all anticancer drugs may exert negative effects on heart, and the most serious complications include the development of left ventricular systolic dysfunction and heart failure [3]. Systolic dysfunction and heart failure are quite close, but not identical terms. Systolic dysfunction refers to the impairment of cardiac contractility whereas heart failure is a clinical syndrome with its certain symptoms and signs: fatigue, dyspnea, swelling etc. Systolic dysfunction is a basis of heart failure, though in some cases, systolic dysfunction may be asymptomatic.

The most severe left ventricular systolic dysfunction is caused by antitumor antibiotics – anthracyclines. Systolic dysfunction and heart failure associated with anthracyclines imply anthracycline-induced cardiomyopathy. Systolic dysfunction may also be induced by other anticancer medications (cyclophosphamide, monoclonal antibodies, and tyrosine-kinase inhibitors), but the cardiac dysfunction in anthracycline-induced cardiomyopathy is the most prominent one and has the poorest prognosis.

There are two major types of cancer treatment-related systolic dysfunction based on toxicity mechanisms of the agents used. Anthracycline-induced cardiomyopathy is a prototype of type I ("damage-related") irreversible injury. Type I dysfunction is characterized by myocardial injury that is accompanied by loss of cardiomyocytes and release of markers of cardiac necrosis; the cardiotoxic effect is dose-dependent. Myocardial damage is generally irreversible; however, early treatment may help in partial recovery of cardiac function. Even if the recovery of cardiac function is achieved, the re-administration of anthracyclines is contraindicated due to an extremely high probability of the recurrence of very aggressive and refractory cardiomyopathy [4, 5].

A number of agents do not directly cause cell damage. Trastuzumab-induced cardiac injury (caused by monoclonal antibodies to ErbB2 receptors) is a prototype of type II ("functional") reversible dysfunction. Other agents that can induce type II dysfunction include: tyrosine kinase inhibitors (lapatinib, imatinib, and sunitinib); a kinase inhibitor, sorafenib; monoclonal antibodies (pertuzumab and bevacizumab); a proteasome inhibitor, bortezomib [6]. Type II dysfunction is not associated with cardiomyocyte death or any detectable structural myocardial changes. The risk of cardiac dysfunction is not dose-dependent; the myocardial damage is frequently (albeit not invariably) reversible and vanishes after the drug discontinuation usually within 1–3 months [4]. The re-administration does not usually lead to the recurrence of the left ventricular dysfunction (if re-admitted after the recovery of the left ventricular function and with the concomitant cardiac protective treatment). Nevertheless, if cardiomyopathy reoccurs, the anticancer drug should be discontinued.

The distinction of type I and II cardiomyopathy basing on the reversibility of cardiac function is rather schematic, as e.g. small-molecule tyrosine kinase inhibitors induce cardiac dysfunction which shares properties of both types. The clarification of mechanisms behind cardiotoxicity of anticancer agent is further complicated by the fact that type I and type II agents are often given sequentially and concurrently. Such sequential and concurrent use may increase cell death indirectly by compromising the environment of marginally compensated cells, contributing to the concern that type II agents can still result in cell death at the time of administration [7].

ANTHRACYCLINE-INDUCED CARDIAC CELL DAMAGE AND DEVELOPMENT OF CARDIOMYOPATHY

Anthracyclines result in direct cardiomyocyte loss via apoptosis, diminished contractility, and compromised microvasculature affecting endothelial cells. Furthermore, the effect of anthracyclines on cardiac progenitor cells and fibroblasts reduces the ability of the already compromised heart to recover from additional cardiac stressors or cardiac injuries [8].

The intracellular interaction of anthracyclines with topoisomerase 2β leads to DNA damage and impairment of mitochondrial function. Generation of reactive oxygen species (ROS) in re-

sponse to anthracycline treatment initiate free radical oxidation cascade reactions that affect proteins, lipids and nucleic acids with subsequent cell dysfunction and loss [9]. The diminished expression of the proteins of intracellular calcium-signaling cycle (SERCA2 and Na^+/Ca^{2+} exchanger) due to ROS as well as the anthracycline-induced disruption of normal sarcomere structure and function both result in decreased myocardial contractility. ROS generation in mitochondria takes part in caspase cascade activation via cytochrome C release.

The underlying structural and functional processes of anthracycline-induced cardiomyopathy are the enlargement of the heart and the decrease of ventricular contractility that manifest as heart failure. The initial decrease of the left ventricular contractility can be revealed as early as 2 hours after the first dose of anthracycline [10]. Nevertheless, cardiomyopathy usually occurs after a year or more of the chemotherapy. The delayed extension of cardiomyopathy may be explained partly by the reserve capacity of the heart to increase the contractility of non-injured myocardium (compensatory hyperkinesis) to maintain the normal contractility of ventricles. However, each dose of anthracyclines causes subsequent loss of a new portion of cardiomyocytes, thus depleting the compensatory capacities of the heart, especially when concomitant cardiac diseases exist. Recent studies revealed several sequences of the extension and evolution of anthracycline-induced cardiomyopathy. In the vast majority of cases cardiac toxicity occurs within the first year after the chemotherapy [11]. Cardiac dysfunction progresses slowly, and the later it develops, the more aggressive it becomes [12, 13]. Anthracycline-induced cardiac toxicity may occur during the ongoing chemotherapy, but unlike chronic cardiomyopathy, the acute one has favorable clinical outcome and is usually manifested with arrhythmias, non-specific ST and T-wave abnormalities, asymptomatic decrease in left ventricular ejection fraction or pericardial effusion. Acute cardiac toxicity is not dose-dependent and does not usually progress to heart failure. The term "anthracycline-induced cardiomyopathy" describes an irreversible and progressive delayed heart damage due to and following chemotherapy. Anthracycline-induced cardiomyopathy is the most aggressive type of cardiomyopathies: 2-year mortality rate exceeds 50%, which is worse than the poorest prognosis for the primary disease [5].

RISK FACTORS OF ANTHRACYCLINE--INDUCED CARDIOMYOPATHY

Unfortunately, any patient who receives anthracyclines may develop cardiac dysfunction. The most prominent risk factors include: cumulative anthracycline dose, chest irradiation, the concomitant anticancer therapy (especially with trastuzumab, cyclophosphamide or paclitaxel), and the initial condition of the heart. The prevention strategies, therefore, should be based on lowering the cumulative dose of anthracyclines, the use of liposomal formulations of doxorubicin and early diagnostics and treatment of concomitant cardiac diseases.

The most important risk factor for the development of cardiac dysfunction is connected with the cumulative dose of doxorubicin. A large retrospective study showed heart failure incidence of 3% and 41% in patients who had received a cumulative dose of 400 or 700 mg/m^2 of doxorubicin respectively [14]. Therefore, oncologists usually limit the cumulative anthracycline dose to less than 450 mg/m^2. The risk of cardiac dysfunction increases substantially after exposition to cumulative dose of 200 mg/m^2 [15]. But even lower doses of doxorubicin (< 150 mg/m^2) cannot be considered totally safe, as the risk of doxorubicin-related cardiac toxicity can occur at a rate from 0.2% to 100%, for cumulative doses of 150 to 850 mg/m^2 respectively. The risk of cardiotoxicity is associated with the irradiation dose [16]. However, administering conventional doses of doxorubicin (4 courses of 60 mg/m^2) and using current optimized radiation protocols minimize the risk of heart failure.

The combination of anthracycline with trastuzumab greatly increases the risk of left ventricular dysfunction [17]. Negative cardiac action of trastuzumab is mainly related with the inhibition of the reconstitution of myocardium after anthracycline-based chemotherapy. Trastuzumab affects the recovery of cardiac cells after they have been "stunned" by anthracyclines. These recovery processes depend on the growth stimuli via activation of ErbB2 receptors on the surface of cardiomyocytes. ErbB2 receptors have high affinity to epidermal growth factor, and their activation is essential for the maintenance of normal function of cardiac cells and their sustainability to different pathological factors. The membrane expression of ErbB2 receptors increases shortly after the initiation of anthracyclines; and if a patient receives trastuzumab during this "vulnerable" period, the interaction of trastuzumab with ErbB2 receptors prevents their activation and the recovery of cardiac cells. The co-therapy with anthracycline and trastuzumab is associated with the incidence of severe heart failure of 16%, while a 3-month delay in trastuzumab treatment almost eliminates this risk [7]. The concentration of ErbB2 receptors on the surface of cardiac cells returns to baseline values within 2–3 months after cessation of treatment with anthracycline. Hence, the longer the interval between anthracycline and trastuzumab, the lower the risk of heart failure.

Patients with cardiovascular diseases run a higher risk of anthracycline-induced cardiac dysfunction. The negative prognostic impact of the preceding heart diseases is a result of left ventricular hemodynamic overload (cardiac "stress") which correlates with the severity of initial cardiac dysfunction and leads to the exhaustion of the compensatory mechanisms. To reveal the severity of "cardiac stress", the ejection fraction, left ventricle size and the diastolic function of left ventricle should be assessed. Moderate or severe deviations in these parameters would be associated with a higher risk of cardiotoxicity. Left ventricle ejection fraction of 30–40% is considered moderately decreased and severely decreased if below 30%. The left ventricle is considered moderately enlarged when its end-diastolic volume is 6.4–6.8 cm in males and 5.7–6.1 cm in females, and severely enlarged if it exceeds 6.8 cm and 6.1 cm respectively [18]. Diastolic dysfunction is assumed if the following signs are present: Doppler E/A ratio ≥ 13; pseudonormal or restrictive type of left ventricular filling pattern; left atrial volume ≥ 34 ml/m^2; pulmonary artery systolic pressure ≥ 35 mmHg; left ventricular mass index ≥ 149 g/m^2 in males and 122 g/m^2 in females; or permanent atrial fibrillation [19].

Finally, the risk of anthracycline-induced cardiomyopathy is increased in patients with acute cardiac diseases or exacerbations of chronic diseases. The conventional cardiovascular risk factors (smoking, dyslipidemia, low physical activity, diabetes mellitus) also increase the risk of anthracycline-induced cardiomyopathy, especially if more than one is present. The advanced age is another prominent risk factor due to the exhaustion of compensatory (reserve) cardiac mechanisms and the prevalence of cardiovascular diseases and diabetes [20]. Other risk factors include: age below 15 years old, female (especially in children), both obesity and low body weight.

DIAGNOSTICS OF ANTHRACYCLINE--INDUCED CARDIOMYOPATHY

The diagnostics of any type of heart failure, including the one caused by anthracyclines, is based on verification of certain symptoms and signs. The symptoms include: exercise intolerance, fatigue, orthopnoea, night attacks of cardiac asthma, night cough, rapid weight gain. The signs comprise gallop cardiac rhythm, expanded neck veins, peripheral edema, crackles, pleural effusion, tachycardia, tachypnea, liver enlargement, ascites. However, the symptoms and signs of heart failure generally appear on advanced stage of anthracycline-induced cardiomyopathy – when cardiac injury is severe and irreversible. The initialization of cardioprotective treatment in this case may not bring obvious prognostic benefits.

The comprehensive diagnostic method to establish anthracycline-induced cardiotoxicity encompasses histopathological examination of myocardial biopsy species, which reveals cytoplasmic vacuolization, myofibrillar degeneration, interstitial edema and mitochondrial deformation. The histological examination has high sensitivity (thus allowing for early detection of cardiotoxicity, long before the first clinical signs) but relatively low specificity. The implementation of non-invasive cardiac imaging diagnostics has decreased the need for myocardial biopsy for verification of anthracycline-induced cardiomyopathy.

The diagnostics of cancer treatment-induced cardiomyopathy is based on the dynamic evaluation of left ventricular ejection fraction (LVEF). The ejection fraction can be estimated by echocardiography, scintigraphy or cardiac magnetic resonance imaging. Magnetic resonance imaging gives the most accurate evaluation of LVEF.

Various criteria for determining cancer therapy-related cardiac dysfunction have been suggested [21–25]. According to the Joint Recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging (2014), the decline in LVEF by > 10% from baseline accompanied by the absolute value below 53% implies the cancer therapy-related cardiac dysfunction [6]. The decrease in ejection fraction may be reversible (within 5 percentage points of baseline), partially reversible (improved by ≥ 10 percentage points from the nadir but remaining > 5 percentage points below baseline) or irreversible (improved by < 10 percentage points from the nadir and remaining > 5 percentage points below baseline).

The most available, cost-effective and safe method for the evaluation of LVEF is echocardiography; however, such limitations as intra-operator or inter-operator variability affect its accuracy. The 10%-variance in LVEF estimated with echo examination is considered acceptable. Therefore, only serial measurements of LVEF represent the left ventricular contractility or its dynamics. According to Armstrong et al., 2D echocardiography had a sensitivity of 25% and a false-negative rate of 75% for detection of LVEF < 50% compared with cardiac magnetic resonance imaging [26]. 3D echocardiography provided higher sensitivity (up to 53%), and should be preferred for LVEF measurement. Nevertheless, even an accurate estimation of LVEF has limited significance as the decrease of ejection fraction (EF) is associated with advanced stages of anthracycline-induced cardiomyopathy. The detection of myocardial dysfunction on the earliest and convertible stages of cardiomyopathy is a challenge of tremendous clin-

ical importance. Cardiac ultrasound speckle tracking with the global left ventricular longitudinal strain evaluation as well as blood tests for cardiac troponins are the most promising areas of such diagnostics [27].

The global longitudinal strain (GLS) is an echocardiographic measure which derives data for deformation and rate of deformation for each of 17 myocardial segments. The decline of GLS by > 15% from the baseline is considered abnormal while the reduction by < 8% from the baseline appears incidental [28]. GLS is an independent, early predictor of later reduction in LVEF and heart failure [29]. Normal GLS is above 16%, which means that each of the left ventricular segments shortens by at least 16% during systole, as compared to its diastolic length [30]. However, reference values for GLS depend on the version of the analysis software and the provider, and different echocardiography machines or software packages can in fact produce different results, making intra-individual comparisons problematic over time. There is also some concern that strain values may decrease with age. It is recommended to use the machine and software version of the same provider to compare individual patients with cancer when using GLS for serial evaluation of systolic function [6].

The administration of anthracyclines is always associated with the loss of a certain number of cardiac cells. If this numer exceeds a critical level, it can be revealed by a test for cardiac troponins. Troponin I (TnI) is a sarcomeric protein and is released following cardiomyocyte death correlating with the severity of cardiac injury. Clinically significant is the elevation of high-sensitive troponin I > 30 pg/ml. The increased troponin I serum level is another reliable marker for the subsequent decrease in ejection fraction associated with anthracycline-induced cardiomyopathy. The test for cardiac troponin should be performed within the first 2 days of each anthracyclines course [31, 32]. The advantages of the test include high negative prognostic value and reproducibility. However, the ambiguity in optimal test periodicity and cut off values limit its significance. Troponin blood level assessment accompanied by GLS evaluation increases diagnostic accuracy in prediction of subsequent decrease in LVEF. Sawaya et al. demonstrated that a negative predictive value of these two noninvasive tests allowed for a confident (97%) exclusion of cardiotoxicity detected by LVEF. In contrast, patients who demonstrated either a decreased longitudinal strain or elevations in high sensitivity TnI had a ninefold increase in risk of cardiotoxicity [33].

ALGORITHM FOR CARDIOLOGICAL MANAGEMENT OF PATIENT RECEIVING ANTHRACYCLINES

The primary goal of cardiac assessment of a patient receiving anthracyclines is the earliest detection of cardiac dysfunction, because the possibility of cardiac recovery depends on an opportune anthracycline discontinuation and cardioprotective treatment initiation. According to the algorithm presented in 2014 by the American Society of Echocardiography and the European Association of Cardiovascular Imaging, all patients before administration of anthracyclines should undergo cardiologic examination encompassing the measurement of LVEF, GLS and serum troponin. The tests should be done prior to the start of chemotherapy, immediately after the treatment and once a year thereafter [6].

An abnormal result of any of these tests indicates the need for a consultation with a cardiologist. Due to the tremendous clinical importance of EF decline below 53% in this group of patients, confirmation in cardiologic magnetic resonance (CMR) should be considered a reference standard for the assessment of LV volumes and LVEF. If the subclinical left ventricular dysfunction is revealed (normal LVEF but disturbed GLS or troponin level), the anthracycline-based therapy may be continued along after initiation of cardioprotectective treatment and careful control of cardiomyopathy signs. A cardiologic follow-up is recommended at the completion of therapy for regimens including doses < 240 mg/m^2. After exceeding the dose of 240 mg/m^2, an evaluation should be performed before each additional course. If the tests reveal the decline in EF by > 10% from baseline accompanied by the absolute value below 53%, the anthracycline-based therapy should be discontinued and the patient should be referred to a cardiologist [6].

Cardiovascular evaluation of patients before and during cancer therapy should be based on the baseline cardiovascular risk profile. In elderly patients with ejection fraction close to the lower reference range or persistent cardiovascular diseases, and in those receiving high doxorubicin equivalent doses, screening should be performed more often and preventive approaches, such as cardioprotective treatment, should be considered [34]. Concomitant cardiovascular diseases should be monitored and treated during each step of the therapy course.

Anthracyclines may still be used in patients with initially decreased ejection fraction, provided that cardiovascular state is stable and there is an absolute need for anthracycline-based therapy; however, cardioprotective treatment as well as compre-

hensive cardiologic assessment prior to each course of treatment have to be considered. If the decline in EF is > 10% from baseline, accompanied by the absolute value below 30%, the anthracycline-based therapy should be discontinued [35].

PREVENTION OF ANTHRACYCLINE--INDUCED CARDIOMYOPATHY

Poor prognosis of anthracycline-induced heart disease raises the need for preventive approaches. They are based on the efforts to decrease the toxic effects of anthracyclines and to enhance the protection of the heart. The first group of approaches includes dosage regimen modification and the use of liposomal formulations of anthracyclines. The second group indicates prompt initiation of cardioprotective treatment.

The modification of the doxorubicin dosage regimen is a simple but still effective method to decrease the risk of cardiac dysfunction. The cardiotoxic effect of doxorubicin is associated with the peak blood concentration, whereas its anticancer efficacy depends on the average plasma concentration (area under the concentration curve). Therefore, in order to decrease the peak concentration of doxorubicin and reduce the risk of cardiac dysfunction, the dosing schedule may be changed to increase the frequency of drug administration (20 mg/m^2 once a week instead of 60 mg/m^2 once in 3 weeks) or decrease the rate of the infusion (continuous infusion for 48–72 h instead of bolus administration). Both of these approaches do not alter the average concentration of doxorubicin, therefore, anticancer efficacy of the drug remains the same [36, 37].

High level of evidence for the prevention of chemotherapy-induced cardiotoxicity was established for iron chelator dexrazoxane, which provided long-term cardioprotection. Historically, the protective role of dexrazoxane was explained by iron chelation that affects anthracycline-induced iron-mediated redox cycling and cytotoxic generation of ROS. However, the ability of dexrazoxane to target topoisomerase 2β and thereby to prevent doxorubicin top2-mediated DNA damaging activities is now considered the main mechanism [38]. A meta-analysis of 10 randomized clinical trials with more than 1600 breast cancer patients has shown that preventive treatment with dexrazoxane reduced the risk of heart failure by 82% [39]. But the concern that dexrazoxane may compromise the anticancer efficacy of anthracyclines limit its approval to patients only with advanced stages of breast cancer who need further anthracycline therapy after having already received 300 mg/m^2.

Patients with a high risk of anthracycline-induced cardiomyopathy (advanced age, concomitant cardiovascular diseases and decreased ejection fraction) should preferably receive pegylated liposomal doxorubicin instead of usual drug formulation. Liposomal doxorubicin is a system containing high doxorubicin concentration inside a particle enclosed with phospholipid bilayer. During circulation in plasma, the drug is predominantly sequestered in liposomes. Liposomes are of larger size than free doxorubicin and cross the endothelial barrier of the microcirculatory vessels of normal tissues and organs, including heart, to a lesser extent. Moreover, the prolonged distribution time increases the ability of liposomal doxorubicin to accumulate in tumor where the permeability of endothelium is higher [40]. Polyethylene glycol coating protects liposomes from phagocytosis, which also elongates the presence of doxorubicin in blood and facilitates its accumulation in tumor [41]. The unique pharmacokinetic characteristics of pegylated liposomal doxorubicin resulted in better safety profile together with anticancer efficacy [42].

For high risk patients of anthracycline-induced cardiomyopathy and for patients with subclinical left ventricular dysfunction (defined by an increased troponin I value or decreased GLS), ACE inhibitors, angiotensin receptor blockers, and β-blockers were shown to effectively prevent the ejection fraction decline and the development of heart failure [43–47]. Whether β-blockers, ACE inhibitors, or angiotensin receptor blockers are useful in primary prevention is uncertain, although in recent OVERCOM trial, combined treatment with an ACE inhibitor, enalapril, and β-blocker, carvedilol, prevented left-ventricular systolic dysfunction in patients with malignant hemopathies treated with intensive chemotherapy (in 78% of cases with anthracycline) [48]. As for anthracycline-induced cardiomyopathy, there is no specific protocols for management and patients should receive standard therapy for heart failure, including ACE inhibitors (or angiotensin receptor blockers), β-blockers, aldosterone antagonists, diuretics, and glycosides [49, 50]. The subsequent functional monitoring after anthracyclines is important as prompt initiation of heart failure treatment is essential for potent recovery and cardiac event reduction [46, 50].

KEY NOTES

- Prior to cancer treatment, cardiotoxicity risk stratification and clinical screening for underlying or developing cardiovascular diseases are needed, including at least ECG, echocardiography and consultation with a cardiologist.
- Cardioprotective medication with reported benefit for prevention of anthracycline-induced cardiotoxicity should be

considered for patients of high risk and with subclinical left ventricular dysfunction (revealed as GLS decline and/or troponin I increase).

- Prompt therapy (as required) based on standards of care should be initiated for concomitant cardiovascular diseases. For elderly patients with concomitant cardiovascular diseases (i.e. those who may benefit from high-dose anthracycline therapy), pegylated liposomal doxorubicin is preferable due to less cardiotoxic effect.

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Authors' contributions:
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