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LONG-TERM CARDIOVASCULAR COMPLICATIONS IN ONCOLOGIC PATIENTS AFTER ANTITUMOR THERAPY (> 1 YEAR)

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SUMMARY

Oncological and cardiovascular diseases (CVD) hold a leading position among the causes of mortality in many countries of the world, including the Russian Federation [1]. In recent years, a decrease in mortality due to oncologic diseases (OD) is noted around the world thanks to early diagnostics, as well as to the development and implementation of new technologies and therapeutic treatment strategies (chemotherapy, targeted and radiation therapy). Among patients with OD who received chemotherapy and radiation therapy, CVD is one of the leading causes of poor prognosis, including lethal outcomes [2-5]. The long-term cardiotoxic effects of antitumor therapy (chemotherapy, radiation therapy) reduce the survival rate and quality of life of patients who suffer from cancer. Thus, early diagnostics and timely detection of the cardiotoxic effects that follow antitumor treatment is one of the main tasks of cardio-oncology.

Keywords: *cardio-oncology, cardiotoxicity, arterial hypertension, heart failure, oncology, speckle tracking technology, radiation therapy, chemotherapy.*

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INTRODUCTION

Oncological and cardiovascular diseases (CVD) hold a leading position among the causes of mortality in many countries of the world, including the Russian Federation [1]. In recent years, a decrease in mortality due to oncologic diseases (OD) is noted around the world thanks to early diagnostics, as well as to the development and implementation of new technologies and therapeutic treatment strategies (chemotherapy, targeted and radiation therapy). A study by the SEER Cancer Statistics Review analyzed the treatment results of patients with breast cancer (BC) over the period from 1975 to 2016, which showed that the 5-year survival rate following an early-stage diagnosis of the disease in the United States increased from 79% in 1990 to 89.9% in 2015 [3, 6, 7]. The number of surviving cancer patients is expected to increase by roughly 30% around the world over the next decade [8].

Among patients with OD who received chemotherapy and radiation therapy, CVD is one of the leading causes of poor prognosis, including lethal outcomes [2-5]. The most common CVD worldwide, including the Russian Federation, is arterial hypertension (AH). According to the ESSE study, 45.4% of men and 41.6% of women showed hypertension among the population of our country aged 24-64 [9]. For that reason, hypertension is often associated with OD. Thus, according to E. Mouhayar et al., hypertension occurred in 30% of cancer patients [10]. AH may both occur in combination with OD, as well as develop and progress over the course of antitumor treatment. In a retrospective study by Hequet et al., 2004, among 141 patients treated with anthracyclines for lymphoma, 18% were diagnosed with hypertension 5 years after treatment with 60% of them manifesting subclinical cardiomyopathy, indicating that hypertension is a risk factor for cardiotoxicity [11]. Similar data were yielded in another study. Smitz et al. showed that patients with lymphoma and AH who received a combination therapy of (R)-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone), showed a more frequent decrease in LVEF (19.7% of all cases) than patients without hypertension (6.6% of all cases). Analysis of that study also showed that hypertension entailed a delay in ordering chemotherapy, ordering less intensive chemotherapy (CT) and even its cancellation [12]. The results of the above studies, as well as many others, have made it possible to conclude that hypertension is one of the risk factors for the development of cardiotoxicity during antitumor treatment [13].

Mortality in OD patients with CVD may be due to the cardiotoxic effect of antitumor therapy or the progression of previously-existing CVD.

Definition, risks and complications of cardiotoxicity

Cardiotoxicity (CT) is a collective term that encompasses all adverse manifestations of the cardiovascular system (CVS) occurring during or after antitumor treatment. The most common clinical manifestations of cardiotoxicity are left ventricular dysfunction, heart failure (HF), and hypertension [14]. CT can be complicated by cardiac arrhythmias and conduction, myocardial infarction (MI), deep vein thrombosis (DVT), and pulmonary embolism (PE).

Acute, early, delayed (late) CT are discrete [1]. Subclinical CT is also discrete [15].

Acute CT develops in approximately 1% of all patients during antitumor treatment, and is commonly reversible [1]. Early CT develops over the course of 1 year, with so-called delayed (late) CT manifesting after 1 year of chemotherapy treatment and beyond [15]. According to its mechanism of action on the myocardium, chemotherapy is conditionally divided into two types. Type I (irreversible type) includes drugs with a direct toxic effect on the myocardium; these are mainly anthracycline antibiotics. These drugs trigger the process of apoptosis of the cardiomyocytes and promote a reduction in the contractility of preserved cardiomyocytes, all of which leads to irreversible myocardial dysfunction. The degree of myocardial damage depends on the cumulative dose of the chemotherapy drug. Type II (reversible type) includes drugs featuring a partial damaging ability with respect to cardiomyocytes. The degree of myocardial damage in this case does not depend on the cumulative dose of the drug. That group of drugs includes monoclonal antibodies (mainly trastuzumab), kinase inhibitors (sunitinib) and others [1, 16]. Given the high effectiveness of anthracyclines in the treatment of malignant neoplasms, these drugs are included in many treatment regimens for cancer patients.

One of the most common oncological diseases among women is breast cancer, which consistently occupies a lead position in the structure of female mortality. Cardiotoxicity accompanying breast cancer occurs mainly during treatment with anthracyclines (doxorubicin, epirubicin), which form part of the main treatment regimens for the disease. CT predictors have been developed using anthracycline-containing therapy, which, in addition to the predictors listed in Table 1, include the cumulative dose of the drug, as well as the rate and mode of its administration. Since 2016, the A.L. Myasnikov Federal State Budgetary Institution Scientific Research Center for Cardiology at the Russian Ministry of Healthcare has been conducting a study to search for early markers and risk factors of cardiotoxicity in patients with triple negative breast cancer and hypertension treated with anthracycline-containing chemotherapy. In that study, it was confirmed that a

Table 1. Risk factors for the development of cardiotoxicity [1]:

Cardiovascular diseases (CVD)	• Heart failure with a preserved and reduced left ventricular (LV) ejection fraction (EF) • Asymptomatic LV dysfunction • (PV <50 or high BNP) • IHD (verified) • AH and AH with LV hypertrophy • Cardiomyopathy • Heart sarcoidosis • Moderate or severe valve pathology with LV hypertrophy or LV lesion • Severe arrhythmias and perturbations of cardiac conduction
Lifestyle risk factors	• Smoking • Alcohol abuse • Obesity • Sedentary lifestyle
Cardiovascular risk factors	• Age (< 18 years; > 50 years for trastuzumab; • > 65 years for anthracyclines) • Family history of early CHD (< 50 years) • Diabetes • Hypercholesterolemia
Previous tumor treatment with	• Anthracycline antibiotics • Radiation therapy of the chest and/or mediastinum.

Note: AH – arterial hypertension; CHD – coronary heart disease; LV – left ventricle.

large cumulative dose of doxorubicin (anthracycline) causes greater myocardial damage (acute cardiotoxicity), especially in patients with breast cancer (BC) and hypertension [17].

Diagnostics, prevention and treatment of late CT in patients with BC and AH, as the most frequently combined OD and CVD, is not well understood. Lately, special attention has been paid to searching for the most informative predictors of the development of late CT using biomarker definitions, speckle tracking echocardiography, in two-dimensional and three-dimensional modes.

Late cardiotoxicity

Most of the work has been devoted to studying the acute and early cardiotoxicity of chemotherapy. In view of the increased life expectancy of OD patients, it seems important to study the effect of antitumor therapy on their CVS rates over the long term following antitumor treatment in order to improve the prognosis for patients who have undergone such treatment.

Late CT may vary from subclinical myocardial dysfunction to the terminal stage of chronic heart failure (CHF), the development of MI, hypertension and other CVDs that affect the duration and quality of life. It should be noted that most studies of late CT involved patients who had had OD in childhood or adolescence [18-24]. These studies form the basic understanding of the incidence and risk factors of late CT.

One of the largest such studies in the United States, which included 14,000 patients treated for OD of various localizations between 1970 and 1986, showed that group of patients to have subsequently manifested a decrease in life expectancy in combination with high risks of developing chronic noncommunicable diseases [56-57].

It was shown in a retrospective study that 15–25 years after their childhood or adolescent treatment for malignant neoplasms (of different localization), such patients demonstrated a CVD mortality rate 8.2 times higher than that of their peers [25, 26]. In their study of 14,359 patients who had undergone OD antitumor treatment, Armstrong G.T. et al. also demonstrated a decrease in life expectancy and a high incidence of chronic non-infectious diseases, including hypertension, coronary heart disease and others. For example, a 24-year-old patient who had suffered cancer in childhood had a life-threatening or fatal-event rate similar to that of his 50-year-old brother. These authors demonstrated that 35 years after an OD, the risk of developing heart failure was 10.9 times higher (95% CI 4.5-26.0), as compared to siblings of the same age [20].

A prospective study by Mulrooney D.A., Yeazel M.W., KawashimaT et al. shed light on the main outcomes of CT during later stages, especially in those patients who were treated with anthracycline antibiotics and radiation therapy. Thus, it was shown that the risks were significantly higher in terms of the development of heart failure (OS 5.9, 95% CI 3.4–9.6), myocardial infarction (OS 5.0, 95% CI 3.3–11.9) and valvular apparatus pathology (OS 4.8, 95% CI 3.0–7.6) [27].

In a similarly designed study conducted by Berthe M. et al., 1,474 patients took part who were diagnosed with Hodgkin's lymphoma in childhood. The survey was conducted 18.7 years after the initial diagnosis. That study also confirmed that the risks of MI, CHF in such patients were significantly higher compared to the general population. [21].

In the recommendations by the European Society of Cardiology (EOC), CT entailing antitumor treatment and developing late was presented in the sections «myocardial dysfunction,» «vascular disease» and «valvular apparatus pathology.»

The myocardial dysfunction group includes LV dysfunction and CHF. In patients with OD and a history of anthracycline antibiotic treatment, there remains a lifelong risk of developing LV dysfunction and heart failure [22, 24].

The frequency of developing left ventricular dysfunction (LVD) as a result of treatment with anthracyclines depends on the total dose of the drug. Consider the respective figures for doxorubicin: with a total dose of 400 mg/m^2, the risk of developing an LVD is 3-5%; with a total dose of 550 mg/m^2, the risk of developing LVD is 26%; and with a total dose of 700 mg/m^2 it is 18–48%. For liposomal anthracyclines with a total dose exceeding 900 mg/m^2, the risk of developing LVD is 2%.

The incidence of LVD during treatment with monoclonal antibodies (trastuzumab) may vary from 1.7% to 20.1%. For alkylating agents such as cyclophosphamide, the risk of developing LVD is between 7% and 28% [1].

The development of heart failure with a developed clinical picture may occur 10 years after the therapy taken [28].

According to recommendations by the European Society of Cardiology for treating OD and CT, patients treated with chemotherapy are encouraged to monitor the status of their CVS via heart imaging and the identification of biomarkers to reach an early diagnosis of their subclinical heart failure [1].

The "vascular disease" and "valvular apparatus pathology" disease group includes CT, which is mainly frolic due to radiation therapy (RT). Long-term cardiotoxicity of RT is manifested by atherosclerotic lesions of the coronary bed and degenerative changes in the valvular apparatus.

Several mechanisms of CT development during RT are considered. One of the main ones is endothelial dysfunction (ED) [29]. With endothelial dysfunction, edema of the endothelial cells develops, an increase in the permeability and deposition of fibrin in the interstitium occurs, which ultimately leads to the formation of fibrosis. An increase in superoxides and peroxides is another cascade of reactions that forms endothelial dysfunction via the production of reactive oxygen species [30] and the nuclear "kappa bi" factor (Nf-kB) [31]. In addition, cytokines and growth factors (the transforming growth factor β1 (TGFb1) and interleukin 1β (IL-1β)) can stimulate endothelial proliferation, fibroblast proliferation, collagen deposition and fibrosis, leading to the progression of vascular lesion in the vascular wall [32]. All of these reactions form secondary systemic inflammation with an increase in the level of pro-inflammatory cytokines IL-6, C-reactive protein (CRP), tumor necrosis factor-α, interferon-γ, and anti-inflammatory cytokine IL-10 [33].

In the irradiated coronary arteries, the proliferation of intima and fibrosis lead to a narrowing of the lumen; in them, loss of smooth muscle cells and adventitious fibrosis are more often observed [34]. The combined effect of radiation and traditional CVD risk factors can significantly accelerate the atherosclerosis induced by RT [35].

Pathology of the valvular apparatus evolves as a result of endothelial damage and the fibrosis of its tissues triggered by mechanisms identical to those involved in vascular lesions under RT. In addition, radiation therapy is a powerful stimulant for pro-calcining factors, such as osteopontin, RUNX2 and alkaline phosphatase, which regulate the metabolism of calcium; it all results in the destruction and calcification of the valvular apparatus [36].

Therefore, even in the absence of symptoms, patients with a history of mediastinal radiation are recommended to undergo an examination to detect CAD [1] 5 years after treatment and every 5 years thereafter, as it may develop within the first 10 years. In patients younger than 50 and those of an older age, the latent period may be longer. In case of breast cancer after RT, the lesion of the middle and distal segments of the anterior descending artery

is most characteristic. With the development of CAD, the risk of death is doubled, and the relative risk of death from myocardial infarction increases by a factor of 2.2–8.8 [37].

It is noteworthy that the section "vascular diseases" in the recommendations of the EOC contains no data on the development or progression of previously-recorded hypertension in patients with acute OD.

Pathology of the valvular apparatus is quite common: 1% after 10 years, 5% after 15 years, 6% 20 years after RT. The frequency of valvular defects sharply increases 20 years after RT. For mild aortic insufficiency, the frequency is 45%, for moderate and severe it is 15%, for aortic valve stenosis it is 16%, for mild mitral insufficiency it is 48%, for mild pulmonary valve insufficiency it is 12% [37]. The average interval preceding the diagnosis after mediastinal RT is 22 years.

Monitoring of the structural and functional state of the heart by the method of transthoracic echocardiography (EchoCG) in patients who received RT as a result of OD should be undertaken 10 years after irradiation and every 5 years thereafter [1, 37].

Diagnostic methods for late cardiotoxicity

The identification of acute and early cardiotoxicity uses the definition of biomarkers, such as: Troponin T, Troponin I; however, they are not informative for the detection of late CT [38]. Determining BNP/NT-proBNP to detect HF is widely recognized [39]. A number of studies have examined the role of NT-proBNP as a non-invasive method for detecting late CT. In a retrospective study, Amal Z. et al. looked into the concentration of NT-proBNP and tissue myocardial dopplerography (TMD) as markers of the development of late CT in 90 patients who suffered from OD in their childhood and received antitumor treatment (anthracycline antibiotics and radiation therapy). Of these patients, 30% showed an increase in NT-proBNP, which correlated with a younger age at the time of diagnosis, a high cumulative dose of anthracycline, and radiation therapy [40]. A similar result was yielded in a study by Sherief et al., which revealed an asymptomatic increase in NT-proBNP in 20% of the 50 surviving patients treated for cancer [41]. Similar results were obtained in another study in which an increase in NT-proBNP was detected in 13% of 122 surviving children with OD within remote periods following antitumor treatment. However, the authors of that study found no significant link between the patients' age and the increase in NT-proBNP. Instead, they saw a clear link of a different nature – that between increased NT-proBNP and a higher cumulative dose of anthracyclines [42]. It should be noted that the authors of the above studies point to an asymptomatic increase in NT-proBNP, which may be regarded as a subclinical stage of heart failure. Moreover, during the years of those studies, no diagnostic criteria for the degree of increase in BNP/NT-proBNP in heart-failure diagnosis had yet been adopted. Studies of the role of NT-proBNP as an early marker of late subclinical cardiotoxicity are still underway today, and that marker may be recommended for screening patients with acute OD who feature a history of anthracycline-containing chemotherapy [1].

Transthoracic echocardiography (TTE) is recommended to be taken both initially (before antitumor treatment) and subsequently as a dynamic follow-up in patients with acute OD. The algorithm for diagnosing the structural and functional state of the heart begins with an assessment of LVEF following the Simpson's Biplan method. According to the European Association for Imaging Methods and the American Society of Echocardiography in Cardiology, a decrease in LVEF by more than 10% off its initial level and a decrease to less than 53% are signs of CT development against the backdrop of antitumor treatment [43]. The diagnostic criteria for CT EOC differ slightly: a decrease in LVEF by more than 10% of the initial level and its drop below 50% [43]. However, it was shown that LVEF is not sensitive enough to detect early changes (subclinical CT) in myocardial contractility [44]. The speckle-tracking echocardiography (STE) technology used recently in its two-dimensional (2D) and three-dimensional (3D) modes is more sensitive to changes that precede a decrease in LVEF [45]. 2D-STE is used to assess the parameters of LV deformation. The most studied deformation parameter is the global longitudinal strain index (GLS). A relative percentage reduction in GLS by more than 15% of the baseline is considered pathological and is a marker of early subclinical LV dysfunction [1]. But a decrease in GLS is not indicative of the need to correct or discontinue chemotherapy. A number of studies continue looking into this indicator. The main limitation of STE technology is a decrease in the method's information content in patients with a permanent form of atrial fibrillation. The advantage of 3D-STE over 2D-STE lies in its comprehensive assessment of all LV deformation parameters (radial, longitudinal and circular) when recording a three-dimensional echocardiographic image from a single apical position. Using 3D TTE, it is also possible to determine such a deformation parameter as the Global Area Strain (GAS) [16]. Currently, this method is not well understood and research is proceeding in that direction.

All patients undergoing antitumor treatment should take an electrocardiogram (ECG) during their routine examination prior to and following chemotherapy. ECG changes are nonspecific for cardiotoxicity. However, when such changes as tachycardia, changes in the ST-T segment, rhythm and conduction disturbances are revealed in that category of patients, these may indicate the development of late CT [1].

One of the cutting-edge methods for assessing the structural and functional state of the heart and detecting fibro-cicatricial changes in the myocardium, which may have prognostic value in relation to impaired LV function, is MRI [1]. However, the differential diagnostics of diffuse fibrosis in case of anthracycline lesions of the heart and those of other genesis using MRI remains difficult. The role of MRI in assessing the cardiotoxicity of antitumor treatment is poorly understood and requires further research.

Prevention and treatment of chemotherapy cardiotoxicity

Currently, drugs are being actively studied to prevent cardiotoxicity. Available research data on the classes of drugs are contradictory, but it is worth noting that they are all limited to a small sample group and a short observation span. In a number of studies, cardioprotective properties have been proven with respect to angiotensin II receptor blockers (candesartan, telmisartan), angiotensin-converting enzyme inhibitors (ACE inhibitors) (enalapril) and beta-blockers (carvedilol, nebivolol) [46–50]. In the OVERCOM study, treatment with enalapril and carvedilol prevented the development of CT arising as a result of ongoing chemotherapy [50]. At the same time, the MANTICORE-101 study showed that perindopril and bisoprolol do not prevent LV remodeling in patients with acute OD against the backdrop of chemotherapy [51]. In one of the largest randomized, placebo-controlled trials of PRADA, dedicated to the primary prevention of myocardial dysfunction caused by anthracyclines using angiotensin II receptor blockers, the cardioprotective effect of candesartan was demonstrated. The study included 130 patients with early breast cancer without CVD. Patients were randomized into groups receiving candesartan, metoprolol succinate, a combination of these drugs, and placebo against the backdrop of adjuvant chemotherapy (which included anthracyclines). The LVEF was evaluated as the primary endpoint, as measured by MRI. In the placebo group, the decrease in LVEF

was 2.6% (with a 95% confidence interval of 1.5–3.8); in the candesartan group, it was 0.8% (with a 95% confidence interval of 0.4–1.9). Differences between the groups reached a statistically-significant level (p = 0.026). Metoprolol failed to demonstrate a similar effect [48].

Another randomized, double-blind, placebo-controlled study using ACE inhibitors (lisinopril) and beta-blockers (carvedilol) demonstrated the effectiveness of prophylaxis with these drugs in patients with a history of anthracycline-containing chemotherapy. The study involved 468 women with breast cancer, averaging 51 ±10.7 years of age. Patients were randomized into placebo, lisinopril, or carvedilol groups. The incidence of CT did not differ in the subgroups; however, in patients receiving anthracycline-containing chemotherapy, carvedilol and lisinopril therapy reduced the likelihood of developing CT (the incidence of CT in the placebo group was 47%, in the lisinopril group it was 37%, and in the carvedilol group it was 31%). In addition, CT developed later against the background use of lisinopril (OR 0.53 (95% CI 0.30–0.94; p = 0.015)) and carvedilol (OR 0.49 (95% CI 0.27–0.89; p = 0.009)). With both lisinopril and carvedilol, chemotherapy was significantly less likely to be canceled [52].

To date, the only drug approved by the FDA (Food and Drug Administration) and EMEA (European Medicines Agency) to prevent CT in anthracycline chemotherapy is dexrazoxane, which is a cyclic derivative of ethylenediaminetetraacetic acid. This drug has a cardioprotective effect by inhibiting the 2β-DNA anthracycline-topoisomerase complex. Dexrazoxane is recommended for breast cancer if the cumulative dose of doxorubicin exceeds 300 mg/m^2 or that of epirubicin exceeds 540 mg/m^2 [50]. However, it should be noted that the use of dexrazoxane has a significant limitation, since dexrazoxane reduces the effectiveness of antitumor therapy. Dexrazoxane can only be recommended if it is not possible to replace anthracyclines with other drugs against the backdrop of an already-achieved high cumulative dose. All of the above, along with the need for high doses of dexrazoxane (10 times the dose of anthracyclines), has led to the limited use of the drug. Research is under way to study the combined drug valsartan-sacubitril [53] and ivabradine [54–55] with the aim of the possible prevention of CT.

CONCLUSION

The long-term cardiotoxic effects of antitumor therapy (chemotherapy, radiation therapy) reduce the survival rate and quality of life of patients who suffer from cancer. Currently, it is relevant to study not only early, but also late cardiotoxic effects, as well as their early detection and prevention.

Conflict of Interest: all authors declare the absence of any conflict of interest.

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