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THE STUDY OF THE EFFECT OF RADIATION AND CHEMOTHERAPY ON THE FUNCTION OF THE HEART

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ABSTRACT

The effect of chemoradiotherapy (CLT) on the cardiovascular system has been known since the 70s [4]. The dose-dependent cardiotoxicity of anthracycline antibiotic metabolites has been most well studied [6], which usually manifests itself already during treatment or in the first months and years after its completion.

The most common of the early clinically significant cardiac complications of radiation therapy is effusion pericarditis. Lesions of the coronary arteries, valves, pericardial constriction and chronic heart failure (CHF), caused by progressive sclerotic changes in all structures of the heart, make their debut much later [3].

Key words: cardio taxicity, effect, radiation therapy, drugs.

INTRODUCTION

Modern chemotherapy and radiation therapy make it possible to preserve the life and work of cancer patients for decades. Mortality from cancer is decreasing, and there is a steady tendency to increase survival. With successful treatment of cancer, the prognosis of life is no longer determined by the main one, but by concomitant diseases, and first of all, by the pathology of the cardiovascular system the system. According to statistics, cancer is the cause of death in only half of patients experiencing cancer, whereas one third of them die from cardiovascular diseases (CVD). At the same time, cardiovascular mortality in this group is significantly higher than in a similar age group that does not receive cancer

treatment. This means that the oncological disease itself, as well as the methods of its treatment, increase the likelihood of developing severe heart and vascular diseases. The steady aging of the population of developed countries also increases the likelihood of cancer and diseases of the cardiovascular system. All of the above means that an increasing number of people in the world have cardiovascular and oncological diseases.

Radiation and chemotherapy have a toxic effect on the cardiovascular system [1, 2]. This influence is so significant that it often determines the prognosis of the patient's life. There was a need for a special study of the mechanisms of cardiovascular toxicity, the development of methods for the prevention and treatment of the negative effects of cancer therapy on the cardiovascular system. These are the prerequisites for the creation of a new discipline –"onco-cardiology" or "cardio-oncology" [1-4]. The world's leading cancer centers are dealing with this problem, developing cardio-oncological services and professional training programs in cardiology. The number of publications on this topic is growing every year. In our country, a search is also underway in the direction of cardiology. Several healthcare organizations have created cardio-oncological areas. However, the diversity and narrow focus of the oncological service and cardiovascular centers in our country creates certain difficulties in the development of cardiology.

Based on the publications of recent years, we offer a review of the literature on cardiology. In the first part of the review, we examined the concepts of cardiotoxicity, vascular toxicity of various groups of drugs that negatively affect the cardiovascular system.

Cardiotoxicity

Anticancer therapy can cause angina pectoris, acute coronary syndrome (ACS), cerebral stroke, critical limb ischemia, arrhythmias and heart failure [4]. This means an effect independent of the direct damaging effect of the tumor on the myocardium or pericardium. Chemotherapy, molecular targeted therapy, targeted radiation of the tumor site growth can lead to the death of cardiomyocytes, loss of myocardial contractility, heart failure, damage to the valvular apparatus of the heart, hypertension, coronary spasm, cardiac arrhythmias and conduction, and sudden death. Moreover, the condition of hypercoagulation, which is common for cancer, increases the risk of acute venous and arterial thrombosis. Cancer therapy can lead to such diverse complications from the cardiovascular system that in order to achieve success in treatment, a cardiologist, or rather several experts in the field of diagnosis and treatment of cardiovascular diseases, must be near the oncologist. But, unfortunately, cancer patients and those at risk of developing cardiovascular complications rarely come to the attention of a cardiologist, because they are

usually not included in randomized clinical trials, registries and observational studies. Nevertheless, leading cancer centers are actively studying the effect of chemotherapy and radiation exposure on the condition of the heart and blood vessels. Considerable experience and material have been accumulated, which deserves close study.

Cardiotoxicity is a decrease in blood pressure the inflammatory function of the heart, which occurs during cancer therapy. The definition of cardiotoxicity has changed over time and there is no single generally accepted concept today. [5]. According to this document, cardiotoxicity is a decrease in the left ventricular ejection fraction (LVEF) by 10 absolute percent to values less than 53% associated with chemotherapy, regardless of the presence or absence of clinical symptoms of heart failure. At the same time, other causes of LVEF decrease should be excluded. The decrease in LVEF should be confirmed by repeated examination after 2-3 weeks. With an improvement in LV by 5% or more, they talk about reversible LV dysfunction.

The effect of chemotherapy on the cardiovascular system

Back in the 60s of the last century, it was noted that chemotherapy with anthracyclines (docorubicin and its analogues) causes a decrease in myocardial contractility [6, 8]. Over time, new groups of drugs have appeared, which have different effects on the heart and blood vessels. The use of anthracyclines, cytostatics, tyrosine kinase inhibitors, and antibodies to endothelial growth factor has significantly improved the prognosis for a number of oncological diseases. But unfortunately, without absolute selectivity and stopping the growth of cancer cells, these drugs cause damage to cardiomyocytes, endocardium, and endothelial cells [9-12].

Cardiotoxicity manifests itself in the form of disorders of general and local contractility of the heart, myocardial ischemia, arrhythmias - due to a violation of the repolarization of the heart. Severe manifestations of heart failure can occur months and years after chemotherapy. It became obvious that monitoring patients and searching for early markers of heart damage is becoming the most urgent problem of cardio-oncology.

Traditionally, it was believed that Doxorubicin and other anthracyclines negatively affect the contractility of the heart due to the formation of free radicals. Doxorubicin cleaves the DNA double helix and leads to a violation of transcription in the mitochondria of cardiac cells, and, as a result, the formation of free radicals. However, modern experimental data indicate the direct effect of doxorubicin on the heart with the formation of complexes with Topoisomerase IIß cardi-omiocytes. Under the influence of doxorubicin, vacuolization of cells,

disorganization of myocardial fibers and death (apoptosis) of a part of cardiomyocytes occur [5-8]. Free radicals are not the main cause of damage to heart cells during anthracycline chemotherapy. This probably explains the complete ineffectiveness of antioxidants in preventing cardiotoxicity. The effect of anthracyclines is cumulative, it also depends on the dose of the drug. But the same dose of the drug causes different degrees of heart damage in different people. The degree of negative effects of chemotherapy depends on the initial functional state of the myocardium, the nature of the disease and the type of heart damage, as well as on the individual, including genetic, characteristics of the patient. In general, the probability of developing heart failure increases significantly when Doxorubicin is administered at a total dose of more than 350 mg/m^2 [6, 7]. Cardiac cells do not have a high regenerative capacity.

Dead cardiomyocytes are not replaced by new ones. There are no clinical manifestations in the acute period. The general contractile function of the heart may remain intact for a long time (for years), but, nevertheless, in the long term, heart damage caused by anthracyclines is irreversible, contractile function worsens. This is the so–called type I cardiotoxicity.

There is a large group of chemotherapeutic drugs (tyrosine kinase inhibitors, recombinant monoclonal antibodies, cytostatics) that do not cause dose-dependent cardiomyocyte death. When treated with these drugs, electron microscopy does not show signs of damage characteristic of anthracyclines, in addition, many of them They have been used systematically for years, without obvious effect on the heart muscle. This is excluded in case of type I cardiotoxicity, because due to the cumulative effect it would lead to the death of the patient. Finally, unlike anthracyclines, the withdrawal of drugs allows to restore contractility, which indicates the reversibility of changes in cardiomyocytes. With such a development of events, it is customary to talk about type II cardiotoxi city. Trastuzumab (Herceptin) – recombinant monoclonal antibodies – refers to drugs with a reversible effect on myocytes. Monoclonal antibodies interact with human epidermal growth factor receptors, delaying the growth of both cancer cells and cardiomyocytes. Although the isolated effect of Trastuzumab on the heart muscle is not so pronounced, it is rarely used as monotherapy, and most often in combination with anthracyclines [9, 10]. In such cases, the damaging effect on the heart is even more pronounced, because damaged but potentially viable cardiomyocytes irretrievably die under the influence of anthracyclines [10].

Since the advent of anthracyclines and trastuzumab, many new drugs with different mechanisms of action have been introduced into chemotherapeutic practice, but drugs acting on endothelial growth factor receptors have the greatest

effect on the cardiovascular system. A classic example is tyrosine kinase inhibitors. Clinically, their effect is manifested by a pronounced rise in blood pressure and myocardial ischemia. Vasoconstriction is considered to be the main mechanism through which this effect is realized. It leads to an increase in the preload on the heart, and vasospasm in the coronary bed leads to the formation of foci of cardiosclerosis in the myocardium (depletion of the vascular bed), which as a result leads to cardiac insufficiency [11-14].

Mechanisms of vascular toxicity in cancer patients

Chemotherapeutic drugs can damage not only cardiomyocytes, but also the vascular system, which leads to both acute and long-term consequences. 5-Fluorouracil (5-FU) and its oral precursor capecitabine cause damage to the endothelium and disturbances in the molecular signaling pathways responsible for the tone of the smooth muscle cells of the arteries. They belong to drugs associated with both angina pectoris and OX5-FU immediately after administration causes pathological vasoreactivity [3], which may be manifested by myocardial ischemia [15-17]. Although myocardial ischemia and arrhythmias after discontinuation of treatment with these drugs are most often reversible, there are nevertheless reports of deaths from cardiac arrest during treatment [18].

Cases of ACS development have been reported against the background of Paclitaxel treatment and, to a lesser extent, with the use of Docetaxel, Vasospasm is a key mechanism, and an unidentified coronary artery disease may be a predisposing factor to it. Unlike 5-FU and Capecitabine, when using these drugs, bradyarrhythmias are noted more often than ischemic events [20].

Cisplatin is uniquely associated with acute coronary artery thrombosis, and in some cases with thrombosis in multiple vascular basins [21-23]. Endothelial damage, thromboxane production, platelet activation and aggregation are the main mechanisms leading to coronary thrombosis [22]. Patients receiving platinum-based drugs have an increased long-term risk of coronary heart disease and myocardial infarction (MI). Bleomycin, often used in combination with Cisplatin, can exacerbate endothelial dysfunction, Vinblastine in combination with Cisplatin can cause endothelial apoptosis [23], which increases the vasotoxic potential of such antitumor therapy [20].

Cyclophosphamide has a toxic effect on endothelial cells, causing vasospastic Prinzmetal angina or hemorrhagic peri-myocarditis [14, 17].

Inhibitors of the endothelial growth factor signaling pathway lead to a multiple increase in the risk of acute cardiovascular events [27-30]. These events may occur in connection with endothelial dysfunction and with the contraction of blood vessels, vascular remodeling, inflammatory processes and platelet activation.

The effect on the formation of the neointima in the atherosclerotic plaque and on its integrity is another unique aspect of this class of drugs. In 70% of patients treated with Sunitinib, there is a decrease in the coronary reserve, especially with long-term therapy. In experimental models, sunitinib causes microvascular damage [28] with a decrease in the number of pericytes and capillaries. Such a "depletion" of the vascular pattern can cause cardiosclerosis in the absence of changes in large coronary arteries. A violation of the functional balance due to the separation of endothelial NO synthase, together with an increase in mitochondrial production of superoxides [30] and an increase in endothelin-1 production, may be an aggravating factor.

Sorafenib is associated with corot spasm-coronary arteries, which is even more pronounced than when using Sunitinib [31-33]. In addition, Sorafenib is associated with the progression of coronary heart disease, while according to other data, Sunitinib causes rupture of atherosclerotic plaques due to a decrease in endothelial repair [34]. In the experimental model, against the background of treatment with Sorafenib, there was a deterioration in survival due to induced necrosis of cardiomyocytes [32, 33]. In addition, there is an increased risk of bleeding in patients who are prescribed treatment with endothelial growth factor inhibitors.

The progression of atherosclerosis and an increase in the frequency of ischemic events were observed with the use of tyrosine kinase inhibitors: Nilotinib and Ponatinib [30]. Some patients develop atherosclerosis, even in the absence of CVD risk factors [33-35]. The mechanism of the predominant effect of Nilotinib on peripheral arteries remains unknown. And when using Ponatib, coronary events and complications from the heart are noted more often than damage to the peripheral arteries (PAP) (6.2%, 4.0% and 3.6%, respectively) [29]. In general, arterial thrombosis occurs 3 times more often than venous thrombosis. Finally, there are several reports of ACS and transient left ventricular apical dilation syndrome (Takotsubo cardiomyopathy) during Rituximab therapy [20].

An increase in cardiovascular risk is noted in patients with prostate cancer who undergo antiandrogenic therapy (AAT) with a gonadotropin-releasing hormone antagonist [21-24]. A 25% increased risk of cardiovascular events has been reported in women taking aromatase inhibitors (Anastrozole, Letrozole, Exemestane) [29]. Randomized placebo-controlled studies did not reveal an increase in cardiovascular risk when using Tamoxifen [32], but showed a significant increase in the risk of thromboembolic complications [29]. It is not yet clear whether the chemotherapeutic agents described above affect cardiovascular risk (especially agents with a direct effect on endothelium), stent endothelium and

whether they increase the risk of stent thrombosis. It has been established that the thrombotic effect of drugs like Vinblastine, which stimulate and control the production of thromboxane and platelet reactivity, can be reduced only by high doses of Clopidrogrel [29]. It is known that the use of stents coated with endothelial growth factor reduces the frequency of their thrombosis, but it is unknown whether the suppression of endothelial growth factors in oncology is associated with the opposite effect – an increase in the risk of thrombosis [29]. Any malignant tumor, by itself, can become a risk factor for stent thrombosis. Some tumors, for example, acute promyelocytic leukemia, and myelomas in general, are associated with a high risk of coronary thrombosis [4]. Radiation therapy and cardiovascular diseases

More than 50% of cancer patients receive radiation therapy (RT). Ionizing radiation affects all cells, but endothelial cells are the most vulnerable. In experimental models, atherosclerotic plaques and arterial thrombosis form several days later.

Fibrosis develops over a long period of time, including all 3 layers of the artery wall. Clinical phenomena are diverse - from accelerated atherosclerosis to thickening of the fibrointima, as well as thrombotic occlusion at the sites of injury to the vessel wall [23, 24].

More than 20 years after RT for Hodgkin's lymphoma, more than 20% of patients develop severe stenosis of the mouth of the trunk of the left and/or right coronary arteries. Oral stenoses are sometimes not detected during traditional stress tests [22-25]. Even in the age group of about 20 years, changes in the coronary arteries were observed in approximately one in five [35]. The risk of carotid artery stenosis and ischemic stroke after radiation therapy of nasopharyngeal tumors is increased [27-30]. RT for the treatment of left-sided breast cancer increases the risk of coronary artery stenosis, which is noted on average 5 years after therapy [53]. In addition to vascular diseases, RT affects the microvascular bed, which leads to a decrease in coronary reserve, myocardial ischemia and fibrosis. The risk of carotid artery stenosis and ischemic stroke after radiation therapy of nasopharyngeal tumors is increased [27-32]. A similar mechanism of damage to the peripheral arteries from RT is observed in patients receiving treatment for various malignant tumors of the abdominal cavity and pelvis, although such complications and consequences of RT are less common than complications in the form of coronary heart disease. The mechanisms of radiation damage to peripheral arteries are similar to the mechanisms of post-radiation coronary artery disease.

The risk of ischemic stroke and sleep damage arterial pressure in patients with head and neck tumors who have undergone RT is also increased [28]. The

frequency of such complications in patients with various malignant tumors suggests that RT increases the existing predisposition to the formation of vulnerable and rapidly growing atherosclerotic plaques in the brachiocephalic arteries. There is a positive experience of carotid artery stenting (CSA) in stenoses induced by radiation therapy [26].

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