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THE NEGATIVE EFFECT OF LONG-TERM CHEMOTHERAPY ON HEART FUNCTION

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ABSTRACT

Recovery from chemotherapy can take place in different ways for different patients and depends on several factors, such as the type and dose of chemotherapy drugs used, the duration of treatment, as well as the general state of health and the level of physical fitness of a person. Typically, the immediate side effects of chemotherapy may persist for several days or weeks after treatment and may include fatigue, nausea and vomiting, hair loss, mouth ulcers, and changes in appetite or taste. These side effects can be managed with medications, dietary changes, and other supportive treatments, and they usually go away over time. There may also be long-term side effects of chemotherapy, such as nerve damage, hearing loss and an increased risk of infection, which may persist for months or years after treatment. For those who have received chemotherapy, it is important to monitor these potential long-term effects and receive appropriate follow-up treatment.

Key words: pathogenesis, treatment, cardiogen, arrhythmia.

INTRODUCTION

Cytostatic myocardial injury is not uncommon among patients receiving chemotherapy, especially the elderly. Anthracyclines are in the first place among cardiotoxic drugs. Anthraquinones and, much less frequently, some other cytostatics (cyclophosphane, paclitaxel, etc.) can also have a damaging effect on the heart. The cardiotoxicity of doxorubicin can develop acutely - within a few days or weeks of treatment, and also manifest itself months or even years after the end of therapy. Early toxicity is rare. It is manifested mainly by myopericarditis,

which can progress within a few weeks from the start of therapy. More often, early toxicity develops in elderly patients and patients who have received massive single doses of anthracyclines. Clinically, supraventricular or ventricular arrhythmias may occur, which rarely take on a life-threatening character. The pathogenesis of these phenomena is not fully understood, and symptomatic approaches (antiarrhythmic drugs, potassium preparations) are recommended as therapeutic measures.

Chronic cardiomyopathy associated with the administration of doxorubicin is of great clinical importance.

Chronic cardiomyopathy associated with the administration of doxorubicin is of great clinical importance. This complication is irreversible and potentially life-threatening. The degree of its severity, as a rule, correlates with the total dose of doxorubicin received.

In addition to the dose, risk factors for the development of anthracycline cardiomyopathy also include female gender, childhood age at the start of treatment (especially before 5 years old), a combination of anthracyclines with other antitumor agents (cyclophosphamide or amsacrine), a combination of chemotherapy with mediastinal radiation therapy, hypertension, hypercholesterolemia [6, 7].

Clinically, acute, subacute, chronic and later chronic cardiotoxic effects of anthracycline antibiotics are distinguished. The acute effect of anthracyclines develops at the time of their administration to the patient and is manifested by vasodilation, hypotension and various arrhythmias [1, 6]. This type of cardiotoxicity is quite rare, but it is always accompanied by high mortality. Subacute heart damage is observed for several days or weeks after completion of chemotherapy and is characterized by the development of myo- and pericarditis; chronic - within 12 months and later chronic — after Iodine or more after the end of treatment with the occurrence of rhythm disturbances [2, 4], conduction, enlarged cavities and severe congestive heart failure. A feature of anthracycline cardiomyopathy is the long-term compensation of cardiac function at the initial stages of development and the rapid progression of heart failure up to a fatal outcome after the appearance of the first clinical symptoms. Due to the fact that anthracyclines penetrate the placental barrier well, they can cause myocardial damage even in utero [5].

The severity of cardiomyopathy determines the time interval between the administration of anthracyclines and the onset of clinical manifestations of cardiomyopathy. With a short interval (less than 4 weeks), the prognosis is extremely unfavorable [3, 11,25].

Given the unfavorable prognosis of anthracycline cardiomyopathies, much attention is paid to their prevention. First of all, this is the exclusion of this group of drugs when the cumulative dose for Doxorubicin is 450 mg / m^2 or even lower, if a dynamic ECG study shows a decrease in voltage or changes in the terminal part of the ventricular complex. Some authors recommend reducing the accepted cumulative dose limit to 300 mg/m^2 in patients over 70 years of age or with concomitant cardiac pathology. Another approach is to use a prolonged (48-hour or even 96-hour) infusion of anthracyclines. Some studies have shown a lower cardiotoxicity of this method of administration with preserved antitumor activityplications of radiation therapyUntil recently, myocardial cells were considered as radioresistant tissues, however, using biochemical, morphofunctional and electron microscopic methods, immediate and long-term changes in the myocardium after local irradiation at doses of 5-10 Gy were detected. Later, these observations were confirmed by Fayardo S. and Stewart A., who showed that microcirculation disorders play a major role in the development of myocardiofibrosis [5,7,18,20]. Late radiation injuries usually include the progression of atherosclerosis, which is manifested by coronary heart disease, as well as the development of fibrous changes in the endocardium, myocardium and pericardium, leading to restrictive cardiomyopathy, constrictive pericarditis, valvular defects, rhythm and conduction disorders, hypertension of the small circulatory circle, and, subsequently, to chronic heart failure. Developing changes in the structures of the heart leads to a deterioration in the quality of life and an increase in the mortality of patients from myocardial infarction, life-threatening rhythm disturbances and sudden arrhythmic death

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Classification of radiation injuries

1 Radiation reactions of the cardiovascular system (early changes in the cardiovascular system) are acute pathological changes in the cardiovascular system that occur during radiation therapy or in the near future after its completion, passing through 2-3 weeks independently or under the influence of special treatment.

2 Radiation injuries (late changes in the cardiovascular system) are pathological changes in the cardiovascular system that occur in the long term after

radiation therapy and are characterized by irreversible morphological or functional changes.

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According to experimental data from various authors, a single irradiation of the heart at doses from 1 to 3.5 Gy reveals a change in the function of capillaries [4,9]. Radiation exposure at doses exceeding the threshold increases the permeability of the endothelial layer, damage to endotheliocyte membranes and necrosis with possible thrombosis of capillaries [9]. In a more distant period, cellular depopulation develops against the background of gradual depletion of the proliferation of damaged endotheliocytes with the development of myocardial ischemia and interstitial fibrosis. The main role of the endothelium as an independent cardiovascular neuroendocrine organ is associated with ensuring dilation of the vascular bed in accordance with the need of peripheral muscles and internal organs, including the heart, for adequate blood supply. With prolonged exposure to damaging factors, gradual depletion and perversion of the "dilating" ability of the endothelium occur [8,19,30].

Most authors note that in ischemia, mitochondria are the most vulnerable structures of cardiomyocytes, whereas the presence in mitochondria of numerous enzymes necessary for the oxidation of carbohydrates, proteins and fats, and the coupling of this process with ATP synthesis indicate the exceptional role of mitochondria in the energy supply of cells [8,30].

Fibroblast dysfunction is one of the components of the mechanism of radiation damage, in particular in the pericardium. The long-term period after irradiation is characterized by an increase in fibrous changes in the structures of the heart. The predominance of pathological changes in a particular structure reflects the variety of possible manifestations of radiation-induced heart disease. In the experiment, from the 50th day after local chest irradiation, rabbits in a single dose of 20 Gy begin to develop pericardial fibrosis, pericardial exudation and diffuse myocardial fibrosis, reaching full development by the 90th day and leading to the death of half of the animals 150 days after irradiation [13,35]. Pericardial fibrosis

may result from damage to the endotheliocytes of the pericardial vessels, which leads to the formation of fibrin deposits in the pericardial stroma. The mechanism of radio-induced proliferation of fibrous tissue is closely related to changes in the structural and functional characteristics of cells that ensure its metabolism. It is believed that the increase in collagen-synthetic activity of fibroblasts is largely determined by radio-induced changes associated, apparently, with damage to their genetic apparatus and exposure to biologically active substances.

Thus, during radiation therapy on the mediastinal organs, the structures of the heart receive an irradiating dose sufficient to prevent the development of post-radiation complications.

Clinical manifestations of complications of radiation therapy.

The most common early cardiovascular complication of radiation therapy is early radiation pericarditis, occurring according to various authors from 0.1% to 4% of cured patients. Most often, the symptoms are stopped on their own, sometimes small doses of nonsteroidal anti-inflammatory drugs are prescribed, the effectiveness of which has not been studied in controlled studies.

Late complications of radiation therapy include radiation damage to the myocardium, valves, cardiac arrhythmias caused by damage to the conduction system, constrictive pericarditis, as well as damage to the coronary arteries (rare).

Most of the patients continue to feel satisfactory for a long time after achieving remission, however, instrumental studies reveal the development of significant cardiac pathology in many of them.

The relevance of the development and implementation of such programs in the world literature is discussed [26, 34], however, to date they have not been developed, unlike recommendations for more gentle methods of radiation therapy, examination of patients to detect recurrence of lymphogranulomatosis or the development of new oncological diseases [34].

The rhythm and conduction disturbances detected during ECG are non-specific and, without the use of additional examination methods, are valuable only for monitoring the tolerability of therapy during treatment with anthracyclines.

Echocardiography makes it possible to diagnose anthracycline myocardial damage manifested by systolic dysfunction of the left ventricle [27]. Some researchers believe that changes in diastolic function precede the occurrence of systolic dysfunction of the left ventricle [17] and are manifested by an extension of the time of isovolumic relaxation (VIVR), an increase in the rate of transmittal blood flow into the phase of atrial systole, a decrease in peak E and the E/A ratio. Similar results were obtained by domestic researchers: small cumulative doses of anthracyclines caused diastolic dysfunction of the type of “insufficient relaxation”;

when exposed to high doses, the violation of diastolic function worsened, which was expressed in “pseudonormalization” of the transmittal blood flow, then systolic dysfunction of the left ventricle developed [31].

In the diagnosis of late cardiovascular complications, data on the prevalence of various changes in the structures of the heart among researchers differ significantly, which is probably due to both the improvement of treatment regimens and the improvement of diagnostic equipment that allows for more accurate assessment of changes. [21, 34] Thus, each next stage of the introduction of new therapy regimens should be accompanied by a subsequent study of the ECHO of KG in the relevant patients.

Myocardial scintigraphy is not widely used. Myocardial scintigraphy in patients with anthracycline cardiomyopathy usually reveals polymorphic zones of radioaccamulation of a radiopharmaceutical without a clear localization, allowing to differentiate postinfarction changes from post-chemotherapeutic ones. Unfortunately, when studying the literature, we did not come across any studies that included a large number of studies in patients after CLT lymphogranulomatosis, there are only descriptions of individual cases. [14]

Myocardial biopsy is used in some medical centers. The method is based on calculating the number of altered muscle fibers and formed areas of necrosis, but has not been widely used due to the high cost and technical complexity. [10]

It should be noted that with coronary angiography, the detected stenoses usually do not visually differ from those found in patients with coronary heart disease, without previous chemoradiotherapy. [6]

Anthracycline myocardial damage may be accompanied by an increase in the concentration of cardiac enzymes in the blood plasma - creatine phosphokinase, lactate dehydrogenase, as well as other markers of myocardial damage, in particular troponins T and I. It is known that the levels of troponins in blood plasma increase slightly (significantly less than in myocardial infarction), can persist even for several months after treatment and are predictors of a decrease in the left ventricular ejection fraction.

Currently, much attention is paid to monitoring various biochemical parameters, which are considered the most sensitive and specific in the diagnosis of subclinical heart damage by cytostatics. In particular, it is assumed that an increase in the levels of natriuretic peptides in blood plasma may indicate the cardiotoxic effect of anthracycline antibiotics [13].

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