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Metabolic Disorders in the Myocardia in the Background of Chemotherapeutic Treatment of Breast Cancer and Ways of Correction

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ABSTRACT

In recent years, there has been significant progress in the treatment of breast cancer associated with the development of new chemotherapeutic drugs. More often, they are used in combination with classical chemotherapy regimens, including doxorubicin. Against the background of such combined treatment, a significant increase in the life expectancy of patients was noted, but at the same time, the risk of cardiotoxic action significantly increases. The review provides information on disorders of cardiomyocyte metabolism during anthracycline therapy, discusses the possibilities of pathogenetic treatment and prevention.

Anthracycline drugs, in particular doxorubicin, are still one of the most effective and widely used chemotherapeutic agents [1]. The use of anthracyclines is limited, in particular, by the possibility of developing severe cardiotoxicity, which can be acute or chronic [3,4]. The greatest concern at the present time is chronic cardiotoxicity, which manifests itself even years after the end of therapy. It is accompanied by progressive systolic dysfunction of the left ventricle (LV), leading to irreversible congestive heart failure. [4].

Anthracycline cardiotoxicity is a multifactorial process that leads to apoptosis of cardiomyocytes [5]. Violation of the metabolism of high-energy phosphates is an important cause of the development of both acute and chronic anthracycline cardiotoxicity [6,13,14]. These mechanisms are largely common to many cardiomyopathies. The heart needs a lot of energy to contract. On isolated models of cardiomyocytes, it was shown quite a long time ago that doxorubicin reduces the concentrations of intracellular adenosine triphosphoric acid (ATP) and phosphocreatine (FC) by more than 50% within 24 hours [7] and by 20% when an effective dose corresponding to 70-minute infusion [8].

More than 90% of the ATP used by cardiomyocytes is produced during mitochondrial respiration. Already in the early stages of doxorubicin cardiotoxicity, characteristic pathological changes in mitochondria develop [11].

The heart is able to utilize various substrates to meet its high energy needs. Under normal conditions, the preferred substrate is fatty acids (FA), which provide the production of 60 to 80% of all ATP in the myocardium. However, during the oxidation of fatty acids, approximately 10%

more oxygen is required to produce a certain amount of ATP than during the oxidation of glucose. Cardiomyopathy induced by doxorubicin is associated with a decrease in the utilization of each of the substrates, both fatty acids and glucose [9]. The reduced rate of glycolysis may be due to the action of doxorubicin on maintaining glucose levels and/or on the ability of cells to stimulate its production. Treatment with doxorubicin leads to a transient increase in glucose uptake in cardiomyocytes by approximately 50% within 1 hour, followed by a significant decrease [10]. Another reason for the decrease in glycolysis may be damage to phosphofructokinase, an enzyme that limits the rate of glycolysis.

Doxorubicin causes damage to various stages of cardiomyocyte metabolism, including a decrease in the basal level of phosphates, FA and ATP, a decrease in the oxidative capacity of mitochondria, a change in the utilization of energy substrates, a violation of energy metabolism in the time interval between energy production and consumption of such creatine phosphokinase.

It must be remembered that structural changes in the heart tissue appear much earlier than the clinical manifestations of heart failure. This means that compensatory mechanisms can maintain the function of the heart for a certain time, despite the increasing damage to the myocardium.

Metabolic disorders in clinically pronounced anthracycline cardiomyopathy are in many ways similar to metabolic disorders in heart failure of another etiology. Chronic heart failure (CHF) is accompanied by morphological changes in mitochondria in the form of a decrease in their size and violation of structural integrity [9].

The strategy for correcting metabolic disorders in CHF of ischemic and non-ischemic etiology has been actively studied in recent decades. It has been substantiated that trimetazidine MB, which changes myocardial metabolism due to the reorientation of the metabolic pathway of energy generation from fatty acids to glucose, has the greatest evidence base among drugs with a cytoprotective effect in CHF. Blockade of long-chain 3-ketoacyl-coenzyme-A-thiolase [2] leads to a decrease in FA β-oxidation and an increase in oxidative glycolysis [6].

The clinical efficacy of trimetazidine MB in CHF has been studied in many scientific studies, including the use of positron emission tomography. The results of the analysis of 17 studies, including more than 900 patients, showed a significant increase in the LV ejection fraction during treatment with trimetazidine MB not only in ischemic, but also in non-ischemic etiology of CHF (by 8.72%, 95% confidence interval 5.51-11 .92; $p<0.01$). Data were also obtained on the beneficial effect of trimetazidine MB on the prognosis of patients with CHF [12]..

There are not so many studies on the study of trimetazidine MB in the treatment and prevention of anthracycline cardiotoxicity. Taking into account the mechanism of the occurrence of metabolic disorders during doxorubicin therapy, the idea of primary prevention of cardiotoxic action with trimetazidine MB is promising. So far, this strategy has been tested in only one small prospective study in breast cancer. In a study in 61 patients undergoing chemotherapy, trimetazidine MB demonstrated similar cardioprotective properties with dexrazoxane [12].

Thus, metabolic disorders, in particular, changes in the intensity of FA β-oxidation, the processes of formation of ATP transport and utilization, play a significant role both in the pathogenesis of oncological diseases and in the pathogenesis of the development of the cardiotoxic effect of doxorubicin.

Conclusions:

1. Trimetazidine MB is a metabolic drug with an extensive evidence base in cardiology, which has demonstrated high efficacy and safety in ischemic and non-ischemic CHF.

2. A similar pathogenesis of metabolic disorders when exposed to doxorubicin in CHF, the results of experimental and single clinical studies on the use of trimetazidine MB for the treatment and prevention of the cardiotoxic effect of doxorubicin suggest its high efficiency.
3. The final place of trimetazidine MB in the prevention of myocardial damage during chemotherapy can be established after randomized clinical trials.

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