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Cardiotoxicity Of Anti-Tumor Treatment Of Anti-Tumor Treatment Of Breast Cancer: Challenges And Prospects

[1]JURAYEVA NOZIMA ORIFOVNA, [2]ABDURAKHMANOV MAMUR MUSTAFAEVICH, [3]ABDURAKHMANOV ZUFAR MAMUROVICH, [4]URAKOV SHUKHRAT TUKHTAEVICH

[1.2] Bukhara, Uzbekistan, postal code 200100

Bukhara State Medical Institute named after Abu Ali ibn Sina, Uzbekistan,

Bukhara, A.Navoi str., 1 Tel.: +998(65) 223-00-50 e-mail: info@bsmi.uz

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KEYWORDS

treatment, dynamics, indicators, cardiovascular system, cardiology, health, heart, breast cancer, change, time period.

Annotation

The article discusses the problem of cardiotoxicity that occurs during the use of antitumor treatment and its impact on the cardiovascular system. Various anticancer drugs, including trastuzumab, can cause myocardial dysfunction and heart failure, leading to increased heart morbidity and mortality in patients. Existing diagnostic methods are not always able to identify early signs of myocardial damage, so the introduction of modern technologies is required for the early assessment of myocardial dysfunction and the development of preventive measures. The article highlights the importance of collaboration between specialists caring for cancer patients to prevent and manage cardiotoxicity. Future research should focus on better understanding the mechanisms of cardiotoxicity, developing new diagnostic and prevention methods, and conducting clinical trials to identify effective strategies for the prevention and management of cardiotoxicity. Exchange of experience and training between specialists from different fields of medicine also play an important role in achieving the best treatment outcomes for patients with cancer.

INTRODUCTION

Breast cancer (BC) represents a significant medical and social problem and is the predominant oncological pathology in women (20.9%). Every year, approximately 1,250,000 new cases of breast cancer are registered globally, and about 54,000 cases are recorded in Uzbekistan. This pathology is widespread in almost all developed countries. The maximum incidence rates are recorded in Australia and Switzerland, while the minimum values are observed in China and Japan. Uzbekistan occupies an intermediate position. In 2019, the cancer rate was 74.1 per 100 thousand people. In the overall structure of malignant neoplasms, breast cancer accounts for 12%. Statistical data on breast cancer in Uzbekistan indicate an increase in morbidity and mortality. Thus, the average annual growth rate compared to the current year is 2.54%. The increase in incidence is associated with various factors, mainly with the improvement of diagnostic methods, which make it possible to identify neoplasms in the early stages before the appearance of the first clinical manifestations. The mortality rate has stabilized in recent years, and in some countries it has been declining. In Uzbekistan, at the end of the current year, the mortality rate is 17 per 100,000 population. Improved methods of diagnosis and treatment of breast cancer will lead to increased survival rates over the past 20 years: the 5-year survival rate is 89%, 10-year - 82%, 15-year - 77% [1].

The use of modern innovative drugs and more intensive standard chemotherapy regimens has led to an increase in disease-free survival and life expectancy of patients suffering from cancer. However, the use of certain chemotherapy drugs and the introduction of drug therapies

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such as targeted therapy have caused a number of complications, the most serious of which is cardiotoxicity [2].

Currently, targeted therapy is the most promising direction in oncology, since it allows influencing the key mechanisms of the development of the tumor process with minimal impact on healthy tissue. Targeted drugs are now included in treatment protocols for many different malignancies, fundamentally changing treatment options and patient prognosis. An example of such a drug is trastuzumab, which has been successfully used in the treatment of HER2-positive breast cancer. The action of this drug is based on a complex system of mechanisms that affect receptor expression, signaling, angiogenesis and the immune response [3].

Currently, the Republic of Uzbekistan allows the use of trastuzumab for the treatment of metastatic breast cancer with high levels of HER2 receptor expression as monotherapy after one or more chemotherapy regimens, as well as in combination with paclitaxel or docetaxel. When using trastuzumab as a single drug, moderate effectiveness is observed in the treatment of metastatic breast cancer (the rate of achieving an objective response in the first line of therapy is no more than 30–40%). However, when trastuzumab is combined with various chemotherapy regimens, objective response rates ranging from 24 to 81% are possible. The inclusion of trastuzumab in preoperative chemotherapy protocols significantly increases the frequency of complete morphological regressions and, as a result, improves treatment results in long-term periods. However, increased antitumor effect when using a combination of trastuzumab with chemotherapeutic drugs, especially anthracycline antibiotics, is accompanied by an increase in cardiotoxicity [4, 5]. Even with many years of clinical experience with trastuzumab, the mechanism of its cardiotoxicity is not completely clear. It is important to note that cardiac complications caused by the combined use of trastuzumab with paclitaxel are reversible, in contrast to its combination with anthracycline antibiotics [6, 7].

Published preliminary results from the ESC-COT (Cardiac-Oncology Toxicity) EACVI/HFA Pilot registry showed that in a study of 1294 breast cancer patients, 63.3% received targeted therapy. During follow-up, suspected left ventricular dysfunction was detected in 23 (2.9%) patients. Patients receiving cardiotoxic chemotherapy should undergo cardiac evaluation during follow-up after completion of treatment [8, 9].

To assess the state of the cardiovascular system in oncology, much attention is paid to echocardiographic studies. Echocardiography, including assessment of left ventricular function, is recommended before initiating potentially cardiotoxic anticancer therapy in all patients, regardless of their medical history, to determine baseline risk. Subsequent monitoring depends on the initial risk of cardiotoxicity.

In actual clinical practice, the use of three-dimensional (3D) or contrast-enhanced echocardiography, myocardial Doppler imaging, and strain assessment remains limited due to various objective and subjective factors. Therefore, at the moment, the main method of assessment remains two-dimensional (2D) biplane measurement of left ventricular ejection fraction using the Simpson method [8].

Recommendations for conducting electrocardiography (ECG) both before and during treatment do not cause difficulties in implementation. ECG signs of cardiac toxicity may include resting tachycardia, ST-T changes, conduction abnormalities, QT prolongation, or cardiac arrhythmias. However, these changes are nonspecific and may be associated with other factors.

The study, aimed at assessing the cardiotoxicity of targeted therapy for breast cancer in real clinical practice, had the following goals and objectives:

Analysis of methods for diagnosing cardiotoxicity used in the daily work of an oncology clinic and assessment of their practical value.

To identify the dynamics of available echocardiography (EchoCG) and electrocardiography (ECG) indicators in patients receiving trastuzumab as part of anticancer therapy.

The study was planned to be conducted in real clinical practice to evaluate the effectiveness of diagnostic methods and the dynamics of indicators in patients receiving targeted therapy for breast cancer, especially the use of trastuzumab.

Methods for diagnosing cardiotoxicity used in the daily work of an oncology clinic may include echocardiography and electrocardiography. An

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echocardiogram can evaluate the structure and function of the heart, including left ventricular ejection fraction (LVEF), and an ECG can detect changes in the electrical activity of the heart. The dynamics of these indicators can be used to assess cardiotoxicity in patients receiving trastuzumab.

However, as noted in the provided text, the use of radioisotope cardiac imaging and magnetic resonance imaging in routine practice is limited. In addition, it is noted that the specific timing of laboratory examination after chemotherapy, the upper limit of normal for specific tests and further tactics in identifying abnormal results have not yet been established.

Thus, at present, the main methods for detecting cardiotoxicity of targeted therapy for breast cancer remain ECG, echocardiography with determination of LVEF and a classic physical examination of the patient.

MATERIALS AND METHODS.

In this study, data from 68 outpatient records of patients who were treated in the department of polytherapy chemotherapy of the Bukhara branch of the RSSPMC of Oncology and Radiology for breast cancer (BC) were analyzed. The use of monoclonal antibodies in healthcare practice has only recently become available, so the number of observations has been limited.

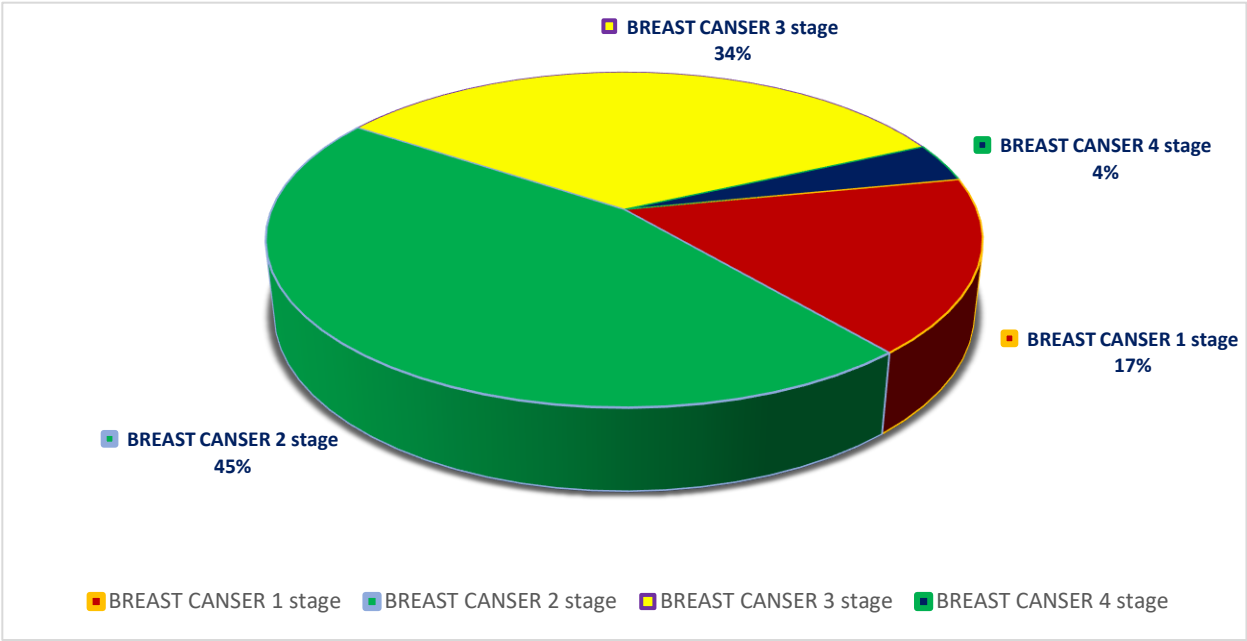

Fig. 1. Distribution of patients by stage of breast cancer

All patients received trastuzumab as monotherapy or in combination with other anticancer drugs. The average age of the patients was 54.2±2.2 years (from 34 to 78 years). Tumor extent was assessed according to the 7th edition of the TNM classification (UICC, 2009). Most patients had stage II (31 people) or stage III (23 people) breast cancer. The distribution of patients by disease stage is shown in Figure 1.

Of the 68 patients with breast cancer, 58.82% (40 women) had pathologies of the cardiovascular system before starting treatment. In the structure of these pathologies, hypertension accounted for 77.5% (31 women) of the total number of diseases. It is important to note that the majority of patients (69%) had the second stage of hypertension with heart damage in the form of left ventricular hypertrophy. In seven patients, hypertension was combined with coronary heart disease, and three patients had chronic rheumatic heart disease.

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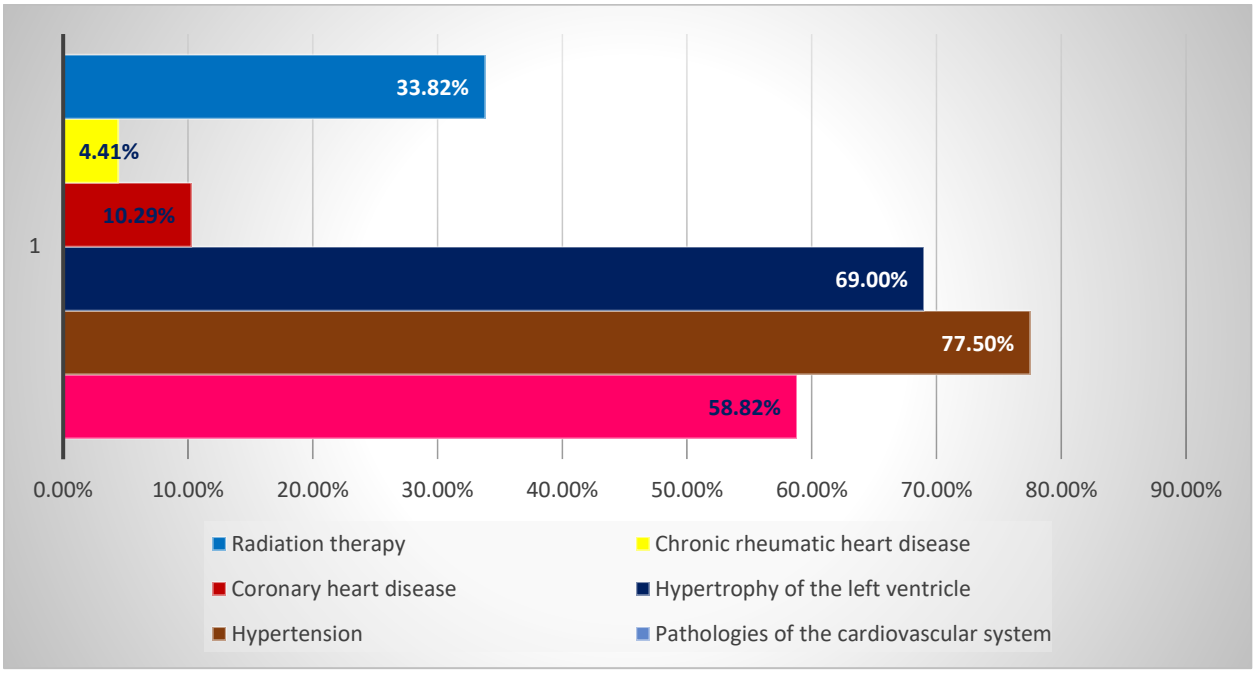

Fig. 2. Distribution of pathologies of the cardiovascular system in the studied patients

In the study, radiation therapy was used in 23 patients, representing 33.82% of the total number of patients.

Of the 68 outpatient records reviewed in the study, only 14 patients (20.58%) did not undergo surgical interventions. Adjuvant chemotherapy was performed in 66.7% of cases.

In 14% of cases, patients received trastuzumab alone. Combination therapy included various antitumor drugs, such as alkylating agents and platinum derivatives, anthracyclines, antimetabolites, hormonal antitumor drugs, herbal drugs, correctors of cartilage tissue metabolism and bisphosphonates.

The average number of courses of therapy with trastuzumab was 10.3±1.9.

All patients underwent the necessary diagnostic studies, including ECG and EchoCG, to assess the state of the cardiovascular system. The dynamics of indicators were assessed at the main control points: before the start of chemotherapy, 1, 3 and 6 months after the start of treatment. These time points were selected according to guidelines for identifying cardiovascular dysfunction, information in the official prescribing information for trastuzumab, and ESMO 2012 recommendations.

During statistical processing of the data, an assessment was made of whether the indicators belonged to a normal distribution. If the indicators corresponded to a normal distribution, then they were described by the mean (M) and standard deviation (SD). Quantitative measures were assessed using Student's t test for dependent variables. Differences between parameters were considered statistically significant at a two-sided p-value <0.05.

RESULTS AND DISCUSSION.

Before analyzing the study results, it should be noted that all measured parameters remained within the established normal range throughout the observed period. Therefore, the present study can only indicate some of the observed trends, with limited confidence due to the small size of the data and the strict experimental protocol.

The findings support previous studies indicating the cardiotoxicity of trastuzumab, which typically occurs during

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chemotherapy. Analysis of electrocardiographic data showed a response to the chemotherapy course [8].

Significant changes in parameters were recorded at the 3rd month of treatment, as shown in Table 1. Graphical characteristics are presented in Diagram 3.

Table 1.

Changes in ECG parameters during treatment at different stages of time during therapy

Index	Heart rate, beats/min	QT duration, s	QRS voltage, mm
Before treatment	75.9 ± 1.93	0.376 ± 0.005	36.2 ± 1.67
1 month	75.3 ± 1.69	0.375 ± 0.005	35.3 ± 2.19
3 months	78.6 ± 2.15	0.369 ± 0.008	38.6 ± 1.91
6 months	74.5 ± 1.92	0.385 ± 0.007	34.6 ± 2.29

During chemotherapy courses, an increase in mean heart rate (HR) was observed by the 3rd month. The mean QT interval decreased slightly compared to baseline values. However, by the 6th month of therapy, with a decrease in heart rate, there was a tendency to prolong the QT interval.

QRS voltage was estimated in millimeters based on the perpendicular distance between the extreme inferior and superior points of the QRS complex for each lead (I, II, III, aVR, aVL, aVF). Analysis of the obtained values showed a decrease in QRS voltage after the first month of therapy, with a subsequent increase. However, results at month 6 show the lowest values compared to baseline. The characteristics of the ST segment and T wave did not undergo significant changes.

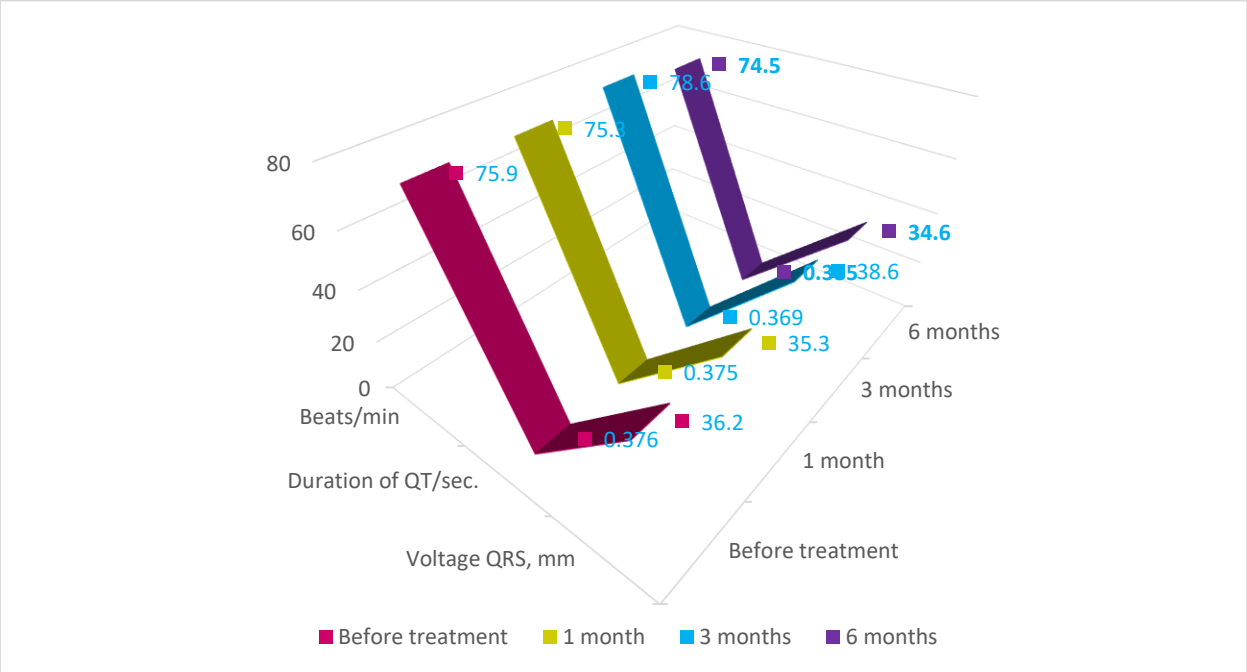

Fig. 3. Dynamics of changes in ECG parameters during treatment at different stages of time

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Regarding rhythm and conduction disturbances, the study noted the appearance of ventricular extrasystoles in two cases and sinus arrhythmia in one case 3 months after the start of antitumor therapy. Subsequently, these violations were successfully eliminated. Initially, four patients were diagnosed with incomplete right bundle branch block, and one patient was found to have intraventricular conduction disturbances that persisted throughout the study period. Three months after the start of therapy, intraventricular conduction disturbances were observed in four patients without further dynamic changes.

It is noted that trastuzumab has a cardiotoxic effect, which manifests itself in an asymptomatic decrease in left ventricular ejection fraction (LVEF) and can lead to the development of dilated cardiomyopathy. Cardiotoxicity is generally considered to occur when LVEF decreases by more than 20% from baseline or any decrease to less than 50%. However, the American Society of Echocardiography uses more stringent criteria to define cardiotoxicity: a decrease in LVEF of more than 5% to less than 55% with evidence of heart failure, or an asymptomatic decrease of more than 10% to less than 55% [2, 10, eleven].

In the presented study, no direct clinical signs of cardiotoxic effect of the protocolized therapy were found. There was a slight decrease in left ventricular ejection fraction (LVEF) during the first month of treatment, followed by recovery by the third month. The final assessment of LVEF after six months of treatment showed a slight difference from the initial values, which presumably indicates the inclusion of compensatory mechanisms for the functioning of cardiomyocytes (Diagram 4).

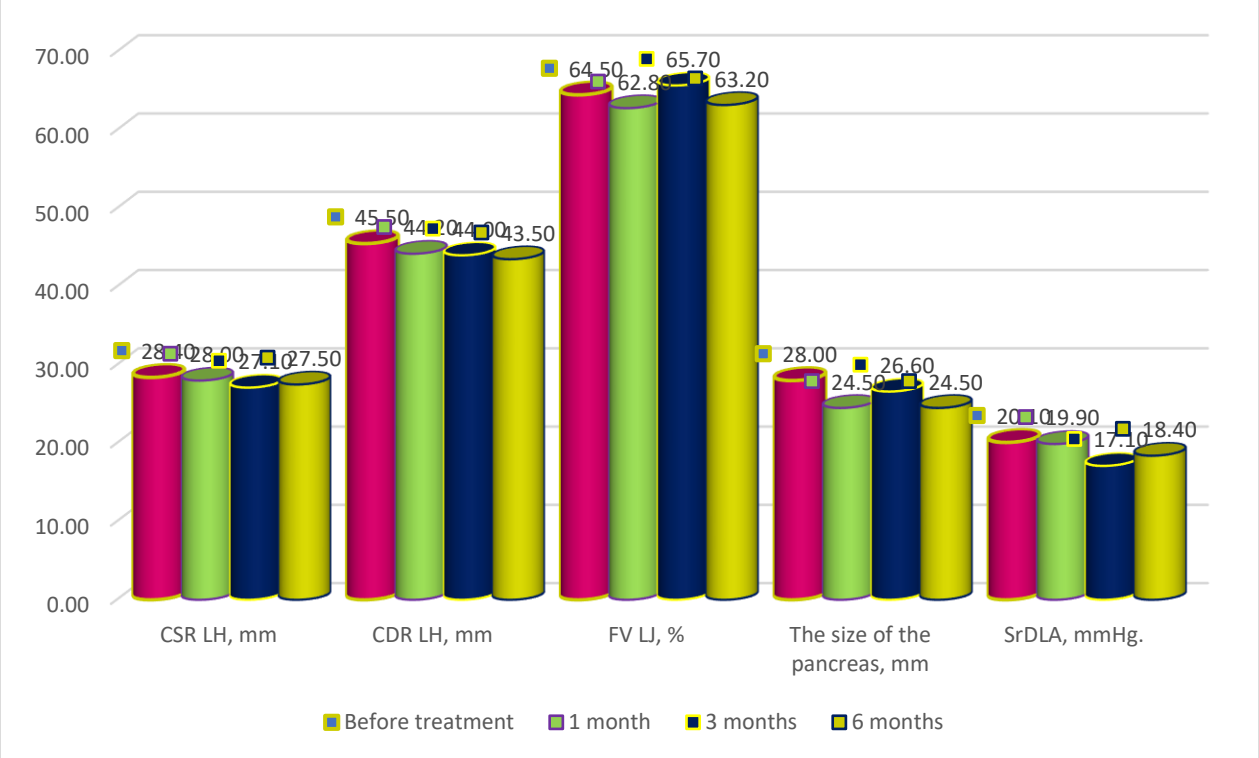

Fig. 4. Dynamics of changes in EchoCG parameters during 6 months of treatment

Moreover, it would be interesting to analyze other available echocardiographic parameters that are widely used in clinical practice. During observation, a slight decrease in the systolic and diastolic dimensions of the left ventricle (LV ESD and LV ESD, respectively) was observed. A study of the size of the right ventricle and mean pulmonary artery pressure

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did not reveal statistically significant changes in these indicators.

The mechanism of action of trastuzumab on the myocardium is not completely clear. It has been suggested that its cardiotoxicity may be due to antigen cross-reaction caused by HER-2 expression on cardiomyocytes. The most studied pathophysiological mechanism of cardiotoxicity is the generation of reactive oxygen species and oxidation of cell membrane lipids, which leads to damage to cardiomyocytes. The damaging effect of trastuzumab is considered reversible due to mitochondrial and protein damage, which does not lead to myocardial death [8, 12].

In our study, we found no clear evidence of irreversible cardiomyocyte damage after 6 months of trastuzumab therapy. On the contrary, we observed positive dynamics in many indicators, which may indicate the inclusion of compensatory mechanisms.

Fluctuations in some echocardiographic parameters are likely due to intracellular damage caused by increased oxidative stress. Myocardial relaxation, based on the function of microfilaments and the sarcoplasmic calcium pump, requires energy, which may be insufficient under the pathological influence of oxidation products. Perhaps the appearance of rhythm and conduction disturbances has a similar etiopathogenetic mechanism. Damage and energy deficiency caused by oxidative stress in the myocardial conduction system lead to disruption of its function and the appearance of functional disorders, which are partially compensated in the future.

CONCLUSION

Myocardial dysfunction and heart failure are serious manifestations of anticancer treatment-induced cardiotoxicity and are associated with increased cardiovascular morbidity and mortality. Existing diagnostic methods used in clinical practice do not provide early detection of myocardial damage. Therefore, the introduction of modern technologies for assessing myocardial dysfunction and developing preventive measures remains relevant. Collaborative efforts among cancer care providers are essential to prevent and manage cardiotoxicity without compromising cancer treatment to maximize overall patient outcomes.

In conclusion, it is noted that further research should be aimed at a deeper understanding of the mechanisms of cardiotoxicity and the development of new methods of diagnosis and prevention. Long-term clinical studies with a larger patient population are needed to determine the most effective strategies for preventing and managing cardiotoxicity. It is also important to provide training and exchange of experience between specialists from different medical disciplines to create multidisciplinary teams that can effectively respond to the risks of cardiotoxicity and provide the best treatment for patients with cancer.

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