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EARLY DIAGNOSIS OF HEART FAILURE IN PATIENTS WITH BREAST CANCER THAT DEVELOPED AS A RESULT OF CHEMOTHERAPY

Specialty: 3218.01 - Cardiology

Field of science: Medicine

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ABSTRACT

of the submitted dissertation to obtain Doctor of Philosophy degree

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The dissertation work was carried out on the basis of the III Department of Internal Medicine, the Teaching Surgery Clinic and the Oncology Clinic of the Azerbaijan Medical University.

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GENERAL CHARACTERİSTİCS OF WORK

Relevance of research: In the developed countries of the world, mortality due to cancer ranks second after deaths caused by ischemic heart diseases. Since the 1990s, there has been a steady decrease in cancer-related deaths, which is associated with a continued increase in cancer survivors[1]. While the progressive development of anti-cancer CDTs enhances the survival of cancer patients, concurrently, it also tends to increase disease and mortality rates due to additional side effects[2]. One of these side effects, particularly the most important, is cardiovascular disease. The occurrence of mortality from cardiovascular diseases in cancer survivors due to the treatment of the primary disease remains relevant today[3]. It is assumed that this severe cardiotoxicity of anti-cancer treatments occurs either as a result of the direct effects of these treatments or as a result of accelerated pathological processes in patients with cardiovascular risk factors[4]. For this reason, interest in cardio-oncology has been increasing in recent years. Many aspects of cardiovascular diseases, especially complications with heart failure, related to anti-cancer chemotherapy are waiting to be clarified with actual questions nowadays. The 2022 European Society of Cardiology (ESC) Guidelines emphasized that this issue is a very actual problem for the healthcare system and recommended further research on this topic in the future[5]. Breast cancer pathology

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is the most common type of cancer in women overall, are diagnosed in 125 of every 100,000 women in the United States of America and approximately 1.4 million women worldwide each year[6]. Over the past 10 years, although the incidence of new cases has remained stable, the death rate started to decrease by an average of 1.8% per year from 2005 to 2014. In 2007-2013 the five-year survival rate was 89.7%[7].

At the same time, it is assumed that more than 3.8 million women living in the United States of America have recovered from breast cancer. In addition, cardiovascular disease is highly prevalent and affects significantly to morbidity and mortality in the United States[8]. Thus, cardiovascular disease-related mortality is higher in older women with breast cancer than in women without breast cancer[9].

Data from the MANTICORE study (45) show that bisoprolol attenuates the reduction in LVEF and thus significantly prevents discontinuation of anti-cancer treatment with trastuzumab. Detection of cardiac dysfunction before or during treatment may lead to changes in the treatment plan or timely additional interventions[10].

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Breast cancer is the main form of cancer pathology in women, mainly in South East Asia, Australia and New Zealand, and in general worldwide[11]. Treatment of breast cancer is based on the use of specific markers, such as tumor estrogen receptor, progesterone receptor, human epidermal growth factor receptor-2 (HER2), and disease stage. Outcomes by combining surgery, chemotherapy and radiation therapy with targeted therapy have improved significantly for the last twenty years. The average five-year survival rate for these events is currently approximately 87%. Prolonged survival has led to increased attention to the off-target effects of breast cancer treatment.

Cardiologists frequently encounter cancer patients in daily cardiology practice due to the prolonged survival time of breast cancer patients due to advances in cancer treatment and the cardiotoxic effects of newly applied treatments in this field. After data on the cardiotoxicity of anthracyclines became available, this led to the development of HER-2-based therapies. This important progress and obtaining of data on cardiovascular toxicity associated with tyrosine kinase inhibitors, led to the formation of the discipline of cardio-oncology. Thus, the ESC published a report article on cardio-oncology for the first time in 2016, and later, during the ESC annual congress in 2022, it published the first clinical guideline recommendation on cardio-oncology. Until the period of guideline recommendation published in 2022, the approach to this issue was at the research level.

Thus, in 2018, when we started the research, we determined the goal of our research, taking into account the lack of research conducted in this field and from the point of view that this topic is a very actual problem in modern medicine.

Object and subject of the research. The object of the research consisted of 120 female patients aged 18 to 65 years who were diagnosed with breast cancer.

The subjects of the research include determination the early diagnosis of heart failure in patients with breast cancer.

The goal of the research. The main goal of the research is to study the early diagnosis of heart failure developed as a result of anti-cancer chemotherapy in patients with breast cancer.

[11] Accessed 30 June 20

Tasks of the research:

1. Studying of cardiac activity before starting and after each course of anti-cancer CDT in confirmed breast cancer patients.
2. Comparative study of cardiac activity immediately after completing anti-cancer CDT for confirmed breast cancer patients who did not undergo cardiology examinations between courses.
3. Studying of cardiac activity one year after completing anti-cancer CDT for confirmed breast cancer patients who underwent cardiology examinations between courses.
4. Comparative study of cardiac activity one year after completing anti-cancer CDT for confirmed breast cancer patients who did not undergo cardiology examinations between courses.
5. Investigating survival in research groups.

Examination methods: Methods such as conducting physical examinations, determining hemodynamic indicators, instrumental examination methods (ECG, transthoracic echocardiography (TTE)), conducting clinical observation, determining the level of NT-proBNP in the blood from laboratory examinations, and statistical analysis were used in the study.

Key Points Presented in Defense:

- As a result of our scientific research, developing heart failure was detected early in patients with breast cancer who received CDT with absolute cardiotoxic effect.
- In research groups, the advantage of regular use of TTE examination and NT-proBNP in early diagnosis of heart failure related to CDT in oncology patients was clarified.
- On the basis of the obtained results, effective practical recommendations were developed and recommended for implementation in daily practice for the early diagnosis of heart failure related to CDT in oncology patients
- Early diagnosis of the heart failure component of chemotherapy-related cardiotoxicity is superior both medically and financially.

Scientific novelty of the research. For the first time, NT-proBNP was regularly used for the early diagnosis of developing heart failure in breast cancer patients undergoing combined CDT.

Taking into account the limited findings in the literature we have researched in recent years regarding the resolution of the problem with the method we propose, the overall results of similar existing research in this direction have been controversial. Thus, the ESC published a a report article on cardio-oncology for the first time in 2016, and later, during the ESC annual congress in 2022, it published the first clinical guideline recommendation on cardio-oncology. Until the period of guideline recommendation published in 2022, the approach to this issue was at the research level.

The key difference of this research compared to other researches up to 2018 is the early diagnosis of developing heart failure related to combined chemical drug treatment (CDT) in breast cancer patients.

Practical significance of the study:

As a result of our scientific research, proposing the regular use of N-Terminal Pro-B-Type Natriuretic Peptide (NT-proBNP) in the early diagnosis of developing heart failure related to CDT in breast cancer patients makes it possible to detect heart failure in early stage. Also, as a result of timely diagnosis, necessary treatment and preventive measures can be carried out in these patients at an early stage, which will prevent death or premature discontinuation of anti-cancer treatment due to timely treatment against the main disease. Irreversible changes in early diagnosis of heart failure are rare, which can be more beneficial both medically and financially.

Thus, in this group of patients, it will be possible to reduce both disability and death rate, and increase survival.

Approval of dissertation materials. The main provisions of the dissertation were discussed in the form of a report in the following events and conferences: "16th UCCVS (International Congress of Update In Cardiology and Cardiovascular Surgery 2020 (2020, webinar), 5th World Congress on Cardiology and Cardiac Nursing 2020 (2020, webinar), 10th national congress of Azerbaijan Cardiology Society (Baku, 2021), 17th UCCVS (International

Congress of Update In Cardiology and Cardiovascular Surgery 2021 (2021, webinar), 6th World Congress on Cardiology and Cardiac Nursing (2021 , webinar), Congress of Innovations in Heart Failure (Baku, 2022), the Atrial Fibrillation Camp (Guba, 2022), International Scientific-Practical Conference on "Cardio-Oncology: modern views of the problem" dedicated to the "Year of Heydar Aliyev" at the Scientific-Research Institute of Cardiology named after Academician C. M. Abdullayev (Baku, 2023).

The dissertation work was discussed at the inter-departmental meeting of Azerbaijan Medical University on 11.05.2023 and at the Scientific seminar on cardiology specialty 3218.01 of the Dissertation Council ED 2.27 operating under Azerbaijan Medical University on 12.01.2024.

Application of research results. The results of the research were applied to the scientific-research plan of the III Department of Internal Medicine of the Azerbaijan Medical University, in the practical activity of the CDT department of the Cardiology and Oncology Clinic of the Teaching Surgery Clinic.

The name of the institution where the dissertation work was conducted. The dissertation work was conducted at the base of the III Department of Internal Medicine and the Department of Cardiology and Oncology Clinic of the Teaching Surgery Clinic of the Azerbaijan Medical University.

Publications: A total of 20 scientific works have been published on the dissertation topic. Among these, 9 are journal articles (2 in international journals, 7 in local journals), and 11 are theses (4 presented at international meetings, 7 at local meetings).

Dissertation Structure and Layout. The dissertation, printed on a computer, consists of 147 pages (189849 characters): introduction (11942 characters), literature review (43836 characters), material and methods chapter (14211 characters), 2 chapters covering personal research results and their discussion (116691 characters), results (2025 characters), practical recommendations (1082 characters), list of references. The literature list included 121 bibliographic sources, including 2 national and 119 foreign language. The dissertation also includes 14 tables and 25 graphics.

MATERIALS AND METHODS OF RESEARCH

The work was performed at the III Department of Internal Medicine, Teaching Surgery Clinic (Baku) and Oncology Clinic (Baku) of Azerbaijan Medical University (Baku) from 2018 to 2022.

Inclusion criteria:

- CDT (combined with anthracycline-containing scheme) conducted patients due to the diagnosis of breast cancer;
- Patients who are clinically stable from a cardiological standpoint;
- Female patients between the ages of 18-65.

Exclusion criteria:

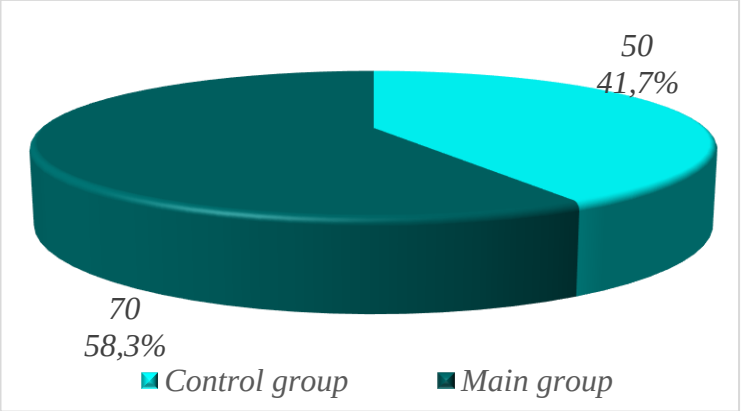
- Patients with cardiac risk factors and structural diseases of the myocardium;
- patients older than 65 years;
- Patients receiving radiation therapy;
- Patients undergoing CDT throughout their life;
- Patients with chronic kidney failure.

Characteristics of patients included in the research. According to the inclusion criteria, 120 breast cancer patients were selected and included in the study from among about 300 female patients suffering from breast cancer. These patients were divided into two groups, each comprising two subgroups (one subgroup consisting of patients aged up to 45 years, and the other subgroup consisting of patients older than 45 years in each group), as illustrated in (graph 1).

The research group (Group I) consisted of prospective patients, comprising 70 women who were diagnosed with breast cancer for the first time, based on their medical records. Patients in this group were studied in the form of subgroups (including 21 patients under 45 years of age and 49 patients over 45 years of age). All patients underwent cardiological examinations both before the start of anti-cancer treatment, and during the inter-course periods of the treatment, as well as one year later the treatment.

The control group (Group II) was formed on the basis of the data of 50 female patients with confirmed breast cancer diagnosis,

who did not undergo cardiology examinations during the intervals between treatment courses. Patients in this group were also studied in the form of two subgroups (including 10 patients under 45 years of age and 40 patients over 45 years of age). All patients in the group also underwent the necessary complex examinations to evaluate cardiac function before starting anti-cancer treatment, immediately after treatment and one year later treatment.



Qraph 1. Design of the research

During examinations, when patients were selected according to the purpose of the study, particular attention was given to the age interval in which they varied. Specifically, it was predetermined that patients should fall within the age range of 18 to 65 years as one of the selection criteria. In general, the minimum age of all patients included in the study was 28 years, the maximum age was 65 years, and the average age was 51,5±0,9 years. In the first group, the minimum age was 28, the maximum age was 65, and the average age was 51,2±1,2. In the second group, the minimum age was 30, the maximum age was 65, and the average age was 51,0±1,3.

Table 1 presents all demographic and clinical indicators of the patients included in the research. As can be seen from the table, the groups did not differ from each other in terms of age, body mass index, risk factors such as obesity, heredity, smoking and diabetes.

The obtained differences between the indicators of the groups were not statistically honest (p>0.05).

Table 1

Demographic and clinical characteristics of patients

İndicators		Groups		Pu
		I group (n=70)	II group (n=50)	
Age, year		51,2±1.2 (28-65)	51,0±1.3 (30-65)	0,530
BMI, kg/m^2		28,4±0,6 (14,7-42,2)	28,8±0,7 (19.4-40,0)	0,776
Obesity	The norm ABC I degree II degree III degree	22 (31,4%) 23 (32,9%) 18 (25,7%) 4 (5,7%) 3 (4,3%)	13 (26,0%) 19 (38,0%) 10 (20,0%) 7 (14,0%) 1 (2,0%)	0,606
Smoking	Smokes Doesn't smoke	68 (97,1%) 2 (2,9%)	50 (100,0%) -	0,230
Diabetes	Have Don't have	5 (7,1%) 65 (92,9%)	4 (8,0%) 46 (92,0%)	0,861
Arterial hypertension	Have Don't have	38(54,3%) 32(45,7%)	26(52,0%) 24(48,0%)	0,805
Heredity	Have Don't have	4 (5,7%) 66 (94,3%)	2 (4,0%) 48 (96,0%)	0,672

Note: Pu - the statistical accuracy of differences between group indicators. (Based on the U-Mann-Whitney measure)

The patients included in the study were randomly assigned to both groups without being distinguished from each other according to the characteristics of pre-existing risk factors.

Among the patients in Group I of the study, 68 patients (97,1%) were noted as non-smokers, while 2 patients (2,9%) were noted as smokers. Among the patients in Group II, smoking is not mentioned at all.

According to the hereditary indicator, among Group I, a total of 4 (5.7%) patients had a family history of breast cancer, and 66 (94.3%) patients had the breast cancer diagnosed for the first time in their family. In Group II, 2 (4,0%) patients had breast cancer in their family history, and 48 (96,0%) patients had breast cancer diagnosed for the first time in their family.

Body mass index (BMI) of patients from both groups was studied. The average BMI of patients in Group I was 28,4 ± 0,6 kg/m2. Regarding this indicator, the minimum value was 14,7 kg/m2, and the maximum value was 42,2 kg/m2. Thus, 22 patients (31,4%) had a normal BMI, 23 patients (32,9%) were overweight, 18 patients (25,7%) were classified as first degree obese, 4 patients (5,7%) as second degree obese, and 3 patients (4,3%) as third degree obese.

The average BMI of patients in Group II was 28,8 ± 0,7 kg/m2. The minimum BMI recorded in this group was 19,4 kg/m2, while the maximum was 40,0 kg/m2. In this group, 13 patients (26,0%) had a normal BMI, 19 patients (38,0%) were overweight, 10 patients (20,0%) were classified as first degree obese, 7 patients (14,0%) as second degree obese, and 1 patient (2,0%) as third degree obese.

Also, 64 of the 120 patients included in the study had arterial hypertension. 38 patients of these were from Group I and 26 patients were from Group II.

Additionally, 9 of the 120 patients included in the study had type II diabetes. 5 patients (7,1%) of these were from Group I, and 4 patients (8,0%) were from Group II.

In the course of the study, attention was also paid to the systolic and diastolic functions of the left ventricle during patient selection. At the beginning of the study, patients with normal systolic and diastolic function of the left ventricle were included in both study groups.

In the complex examination of the patients included in the research were included general clinical, laboratory, and instrumental examinations. In order to clarify the diagnosis and monitor the dynamics of the disease, a detailed medical history was collected in each patient, blood oxygen saturation was measured with a pulse

oximeter, and a complete physical examination was conducted. Additionally, a standard 12-lead ECG was conducted according to accepted protocols, and 2-dimensional Echo, along with color and doppler echocardiography were conducted to evaluate the structural-geometric and functional parameters of the left ventricle in patients. Furthermore, the NT-proBNP level was determined from blood samples. Survival was investigated using the Kaplan-Meier method. In order to evaluate the long-term results, as in the initial protocol, ECG, TTE and blood NT-proBNP level were assigned to each patient.

The period of observation of the patients lasted for 1 year, and the results of the control examinations after 1 year were included in the study.

Electrocardiography: ECG was taken in 12 leads according to the generally accepted procedure. Through this method, the following parameters were analyzed in accordance with standard guidelines: the number of heart beats, rhythm origin, frequency and character, atrioventricular conduction (PQ interval), atrial conduction (P wave), intraventricular conduction (QRS complex), ST segment, ventricular depolarization and late repolarization (QT duration), T wave amplitude and duration, and the bioelectrical activity of the heart chambers.

Echocardiography: Echo, considered the primary examination method for assessing the structure, hemodynamics, and geometric state of the cardiovascular system, was performed using the M and B modes of the *SAMSUNG MEDISON EKO 7* ultrasound diagnostic device manufactured in Korea. The following commonly accepted parameters were measured with this device: left ventricular end-diastolic and end-systolic index, end-systolic and end-diastolic volumes (EDV), ejection fraction using the Simpson method, stroke volume, left atrial indexed volume, pulmonary artery systolic pressure (PASP), left ventricular diastolic function (E/eı , eı, LAVİ, TRvel), and right ventricular systolic function-TAPSE.

For the visualization of cardiac structures, the patient was lying on his/her side and on his back during the entire examination procedure, with his/her head elevated at an angle of 30º. Thus, the

Echo examination of patients allows for a comprehensive evaluation of the functional state of the right and left ventricles (RV and LV), both atria, large vessels and valvular apparatus, segmental and integrative evaluation of the geometric structure of the ventricles, and the contractility of the muscles of both ventricles.

During the examination, practically all structural parts of the heart were recorded. Heart size and functions were evaluated through all echocardiographic windows (parasternal long axis and short axis cut at different levels, as well as 2, 3, 4 and 5 cavity images taken from the top of the heart, suprasternal and subcostal windows). The size and functions of the left ventricular cavity, posterior wall and interventricular septum, and the right ventricle were assessed mainly in the positions drawn from the parasternal long axis and the apex of the heart. A minimum of 5-6 heart rate cycles were recorded in each position and photographed and documented.

Determination of NT-proBNP level in plasma was used as laboratory examination methods. Thus, in recent years, the determination of BNP-level in the blood (NT-proBNP) occupies an important place in the diagnosis of heart failure. 2 ml of blood was taken from the patient's jugular vein and determined by CMIA (chemiluminescent microparticles immunoassay) level of NT-proBNP in plasma using a Siemens Immulite 2000xpi device. In normal plasma NT-proBNP level should be <125pg/ml.

At the end of the study, the Kaplan-Meier method was used to examine survival rates among patients.

Anti-cancer chemotherapy used in patients included in the study:

Patients in the study (120 patients) received CDT with AC scheme as the 1st line:

Cyclophosphamide 600mg/m2, on day 1, with an interval of every 21 days;

Doxorubicin 60mg/m2, on day 1, with an interval of every 21 days.

The medications were administered as follows:

1. 8 mg of dexamethasone is added to 100 ml of isotonic NaCl solution and injected into a vein within 10 minutes;

2. Doxorubicin is added to 100 ml of isotonic NaCl solution and injected into a vein within 20 minutes.
3. After washing the vein with 100 ml of isotonic NaCl solution, cyclophosphamide is added to 500 ml of isotonic NaCl solution and injected into the vein within 30 minutes.

At the end, the vein is washed with 100 ml of isotonic NaCl.

CDT with the AC scheme was carried out with a total of 4 courses every 21 days. Later, these patients are given 4 more courses (TC) of Docetaxel (Paclitaxel) 75 mg/m2 in 250 ml isotonic NaCl solution intravenously for 1 hour and Carboplatin AUC6 in 500 ml NaCl solution intravenously for 30 minutes.

A group of patients underwent 4-6 courses of treatment with the CAF scheme:

Cyclophosphamide 600 mg/m2, on day 1, every 28 days;

Doxorubicin 30 mg/m2, on days 1 and 8, every 28 days;

5-Fluorouracil 500 mg/m2, on day 1, every 28 days.

Or received treatment with the FAC scheme:

Cyclophosphamide 500 mg/m2, on day 1, every 21 days;

Doxorubicin 50 mg/m2 on day, 1, every 21 days;

5-Fluorouracil 500 mg/m2, on day 1, every 21 days.

The administration procedures for the medications were the same.

Cardiological treatments used in the patients included in the study - treatment of heart failure in the main group of patients according to the modern protocol, diuretic, antiarrhythmic, antiplatelet drug (antiaggregant), hypolipidemic, hypotensive means were carried out.

During the research, angiotensin-converting enzyme inhibitors (ACEIs) such as perindopril at daily doses of 2.5-5 mg or ramipril at daily doses of 2.5-10 mg were prescribed to patients with the aim of preventing remodeling.

Additionally, diuretics such as spironolactone at doses of 25 or 50 mg once day, and furosemide at doses of 20-80 mg, were used.

Carvedilol, an alpha and beta adrenoblocker, was prescribed from 6.25 mg to 50 mg, bisoprolol from 2.5 mg to 10 mg per day.

As an antiarrhythmic treatment, ivabradine 10 or 15 mg daily was also prescribed.

During the study, atorvastatin was used as a hypolipidemic agent in a dose of 10-40 mg once a day.

Acetylsalicylic acid in the form of 75 or 100 mg was used for antiaggregant treatment.

The patients included in the control group were also treated according to the modern protocol of heart failure (ACEF/ARB or ARNI, BB, MRB, SGLT2 inhibitors, Diuretic, Ivabradine).

Final evaluation criteria of research results. At the end of the study, patients were evaluated based on left ventricular echocardiographic parameters, plasma NT-proBNP level and mortality (cardiac and non-cardiac deaths), as well as clinical symptoms, number of hospitalizations (cardiac causes).

Mathematical-statistical analysis methods. Research work by design – descriptive and analytical; according to the method - clinical; according to the volume – generalized and selective; according to the type – scientific; according to the material - prospective; according to the duration – transversely and longitudinally; according to location - clinically determined.

Statistical analysis was carried out in the IBM Statistics SPSS-26 software package using variation, discriminant, dispersion and regression analysis methods.

Means for the description of variation series: mean (M), standard error (±m), 95% confidence interval (95%Eİ) and mean structure: median (Me), quartiles (Q1, Q3), largest (max), the smallest (min) indicators, the share amount (%) was calculated for the description of quality indicators.

Non-parametric U-Mann-Whitney and Chi-square Pearson tests were used for longitudinal comparison of ranks. For longitudinal comparisons, W-Wilcoxon and z-Sign measures were applied for 2 points, while W-Kendall and Q-Cochran measures were used for 3 or more points. ANOVA test was conducted to investigate the factor's impact on the final outcome, and statistical accuracy was evaluated with the F-Fisher measure. Kaplan-Meier procedure was applied for default indicators' analysis, and comparison was evaluated using the Log Rank (Mantel-Cox) measure.

OBTAINED RESULTS AND THEIR DISCUSSION

Analysis of the obtained results of the patients included in the research by groups. During the examinations conducted after 1 year of anti-cancer CDT in patients included in the control group of the research, despite 9 patients (18,0%) showing no changes in the T wave and ST segment, 41 patients (82,0%) exhibited certain changes in the T wave and ST segment (pW<0.001). During the detailed evaluation, it was concluded that these changes were not specific.

During the ECG examination, there were non-specific changes observed in the T wave and ST segment in the patients included in the main group of the study. Thus, during the examination of breast cancer patients included in the main group 1 year after anti-cancer CDT, 22 patients (31,4%) in the group had no changes in the T wave and ST segment. However, in 48 (68,6%) patients included in this group, 1 year after anti-cancer CDT, certain changes were noted in the T wave and ST segment, and during detailed evaluation, it was concluded that these changes were not specific.

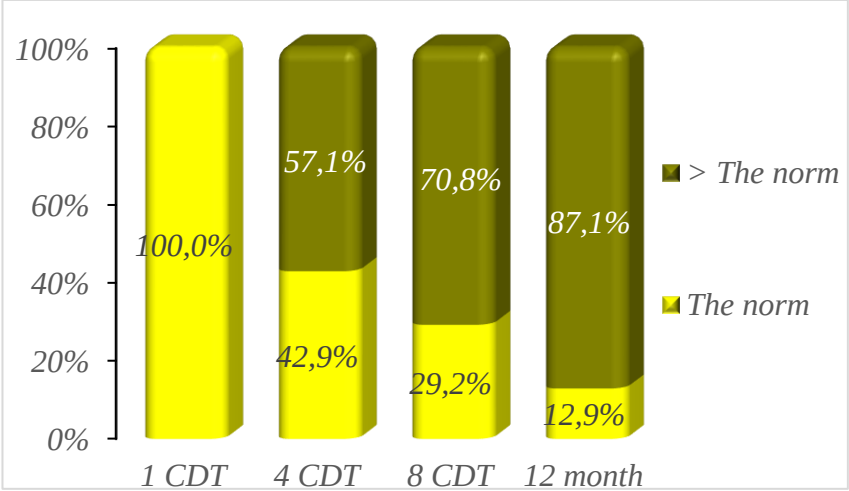
İn 70 patients with breast cancer included in the main group of the research, 11 (15.7%) patients did not have any type of arrhythmia after 1 year of anti-cancer CDT. Of the patients included in this group, 58 (82.9%) patients had sinus rhythm disturbances of different frequencies. Other types of arrhythmias were recorded in only 1 patient (1.4%) in this group. Thus, after 1 year of anti-cancer CDT, various types of arrhythmias were recorded in the majority of patients (pW<0.001).

In our study, when comparing the results of control examinations after 1 year, the level of NT-proBNP was higher in the patients examined in the control group, which can be associated with the lack of necessary control examinations in the period between courses in the patients included in that group.

During the control examinations conducted after 1 year of anti-cancer CDT in the control group patients, the average NT-proBNP level determined in blood laboratory tests for this parameter was 1126,4±100,7 pg/ml.

Among the patients of the main research group, after the 3rd

course of anti-cancer CDT, NT-proBNP level increased in only 1 of the patients included in this group. In this group, NT-proBNP level increased in 40 patients after the 4th course of anti-cancer CDT. After the 5th course of treatment, NT-proBNP level increased in 5 patients included in the group. In the prospectively investigated main group of the study, 21 patients received 6 courses of anti-cancer CDT. NT-proBNP level increased in 8 patients after the 6th course of anti-cancer CDT. 10 patients from this group received 7 courses of anti-cancer CDT. NT-proBNP level increased in only 2 patients after the 7th course of anti-cancer CDT. During the control examinations after the 8th course of anti-cancer CDT of the patients included in the main group, the level of NT-proBNP was higher than normal in 17 patients. The level of NT-proBNP in the blood of all patients was determined during the control examinations of the patients included in this group after 1 year of anti-cancer CDT (graph 2). After 1 year, the average index of this parameter for the group was 501,0±27,1 pg/ml (pW<0.001).



Graph 2. NT pro-BNP levels in the main group after 1 year

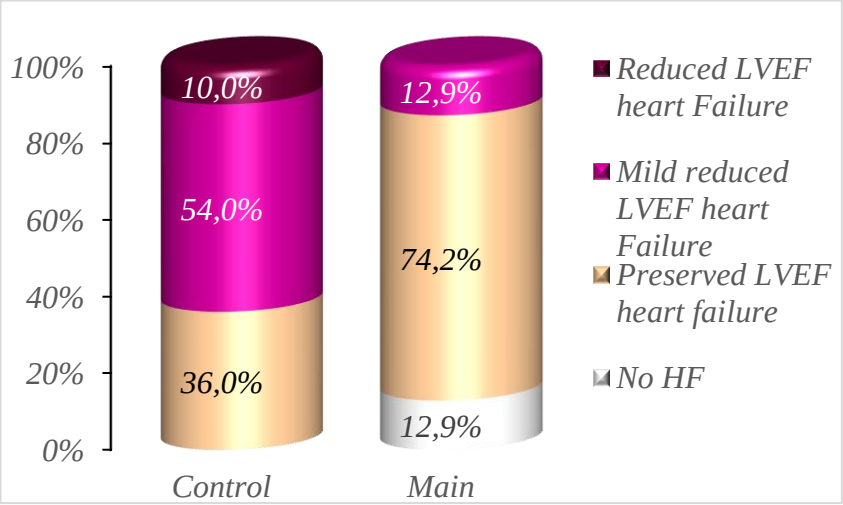
Determination of the level of NT-proBNP in patients at all stages in the main group of our study made it possible to detect heart

failure in patients at the initial stage. At the end of the study, as a result of timely cardiac treatment, the development of heart failure in the main group was found to be weaker than in the control group ($p<0,001$)

During our research, we have widely used the Echo examination method. Echo examination after all treatment courses gave us important information for timely detection of heart failure. So, it was observed that heart failure with preserved ejection fraction occurred in 40 patients from the main group after the 4th course of anti-cancer CDT.

In this group, after the 8th course of anti-cancer CDT, heart failure with preserved ejection fraction was observed in the majority of patients in this group.

In our research's main group, during the Echo examinations and biomarker assessments, timely treatment interventions (ACE inhibitors and beta blockers)in patients with disorders of the cardiovascular system have resulted in superior outcomes compared to the control group (Graph 3).



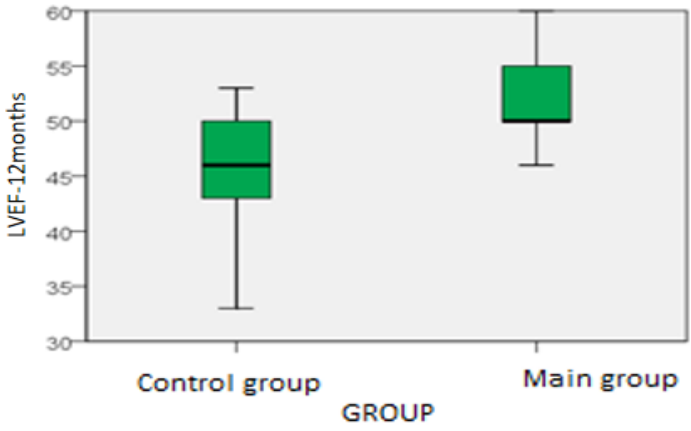
Graph 3. Heart failure index after 1 year

During our study, the main group had less heart failure than the control group as a result of the control examinations conducted between all courses and the timely treatment of heart failure based on their results. Thus, after 1 year of anti-cancer CDT, among the patients in the control group, 36.0% had heart failure with preserved ejection fraction, 54.0% had heart failure with mildly reduced ejection fraction, and 10.0% had heart failure with reduced ejection fraction. Among the patients in our main research group, 74.2% had heart failure with preserved ejection fraction, and 12.9% had heart failure with mildly reduced ejection fraction. So, in the main group, heart failure developed more weakly. During our research, a negative dynamics were observed in the control group as a result of the lack of necessary diagnostic and preventive treatment measures between courses. In the main group of our study, as a result of periodic control examinations and necessary treatment measures, the patients in this group had weak negative dynamics immediately after the anti-cancer CDT compared to the control group in the systolic and diastolic indexes of the left ventricle, as well as in the left ventricular ejection fraction (LVEF).

Thus, the average index of the diastolic size of the left ventricle in the control group was 59,7±0,4 mm after 1 year of anti-cancer CDT. The average index for the main group was 50,5±0,4 mm. Thus, during the control examinations after 1 year of anti-cancer CDT, significant positive dynamics were observed in the majority of patients in our main group in terms of the left ventricle's diastolic measurements ($p < 0,001$). The average index of the systolic diameter of the left ventricle in the control group after 1 year of anti-cancer CDT was 40,3±0,5 mm. In the main group, the average index after 1 year of anti-cancer CDT was 32,3±2,2 mm. A significant level of positive dynamics was observed for this parameter in the patients included in the main group after 1 year of anti-cancer drug treatment ($pu<0,001$). The average index of the EDV of the left ventricle in the control group after 1 year of anti-cancer CDT was 173,5±3,3 ml. The average index of the EDV of the left ventricle in the main group was 136,7±3,2 ml ($pu<0.001$). The average index of the end-systolic volume (ESV) of the left ventricle was 80,9 ± 1,7 ml in the control

group after 1 year of anti-cancer CDT. In the main group, the average index of the ESV of the left ventricle was 63,8±1,4 ml after 1 year of the anti-cancer chemical treatment. During the statistical analysis of the results between the groups, statistical accuracy differences were obtained (pu<0.001).

The average index of the LVEF in the patients included in the control group was 45,5±0,8% after 1 year of anti-cancer CDT. In the main group of patients, the average index of the ejection fraction of the left ventricle was 51,7±0,4% after 1 year of anti-cancer chemical treatment for this group. There were no significant reductions in the contractile function of the left ventricle in the main group, and the average index of this parameter remained within the normal range for the group (p < 0.001) (graph 4). This can be attributed to timely diagnostic examinations and treatment measures conducted in this group during the study.



Graph 4. Comparison of LVEF between groups.

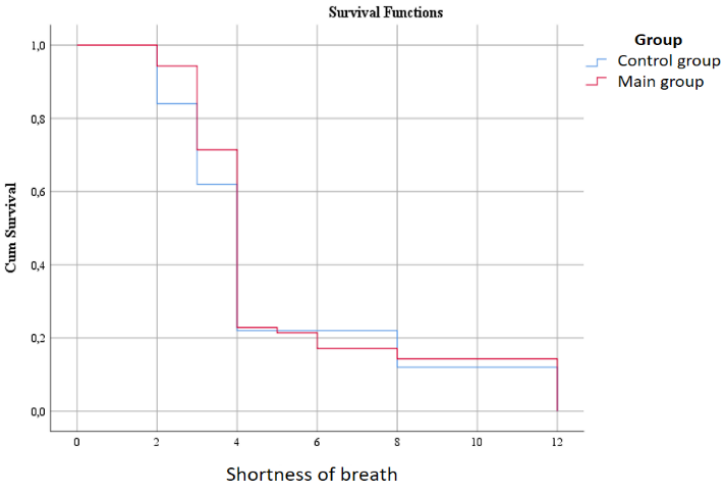
During our research, we used the Kaplan-Meier estimator to clarify both the frequency of occurrence and the duration of identification of various side effects resulting from the anti-cancer CDT conducted on both our control group and the main groups of

patients. When evaluating the results obtained in both the main group and the control group of patients during our research, no statistically significant differences were observed in the analysis of survival rates during the 12-month observation period between patients included in the main group and those included in the control group (p=0,237).

Among the patients included in our study, the average structural indicator of the duration of shortness of breath complaint detection in the control group the median was 4,000±0,146, the lower 95% indicator was 3,713, and the upper 95% indicator was 4,287. In the main group of patients, the average structural indicator of the duration of shortness of breath complaint detection the median was 4,000±0,103, the lower 95% indicator was 3,797, and the upper 95% indicator was 4,203.

Among the control group of patients, the average mathematical indicator of the duration of detection of shortness of breath complaint was – the mean 4,820±0,440, the lower 95% indicator was 3,958%, the upper 95% indicator was 5,682%.

Among the main group of patients, the average mathematical indicator of the duration of detection of shortness of breath complaint was – the mean 5,014±0,365, the lower 95% indicator was 4,298, the upper 95% indicator was 5,731.

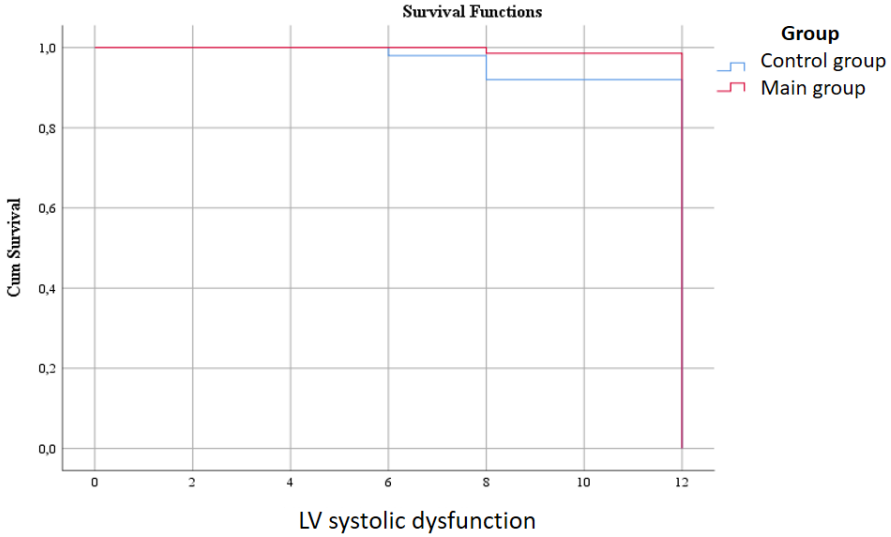


Graph 5. Detection of shortness of breath complaint

There was no statistically significant difference between the groups when evaluating the duration of the of shortness of breath complaint detection (px2=0.453). The graphical description of the results is shown in Graph 5.

Among the patients included in our study, the average mathematical indicator of the detection duration of left ventricular systolic dysfunction in the control group was the mean 11,640±0,178, the lower 95% indicator was 11,291, the upper 95% indicator was 11,989.

In the main group, the average mathematical indicator of the detection duration of left ventricular systolic dysfunction was the mean 11,943±0,057, the lower 95% indicator was 11,831, and the upper 95% indicator was 12,055. There was no statistically accuracy difference between the groups (px2=0,076). Graph 6 shows the results.

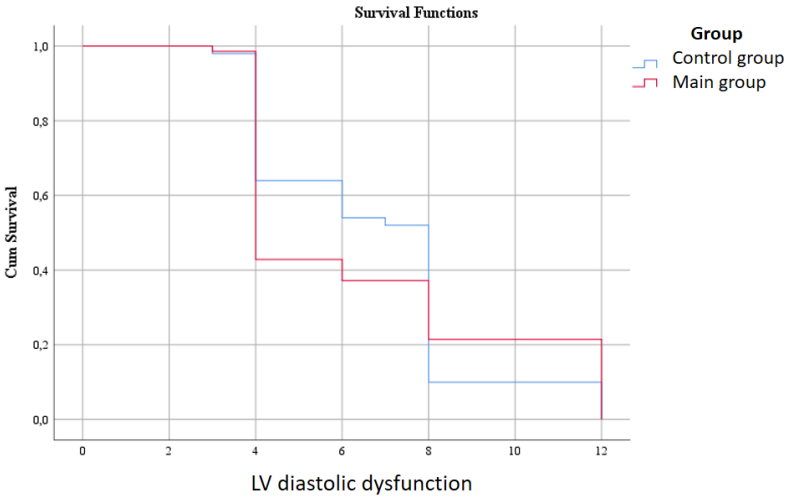


Graph. 6. Detection of left ventricular systolic dysfunction

Among the patients included in our research, the average mathematical indicator of the detection duration of left ventricular diastolic dysfunction in the control group was the mean 6,720±0,359,

the lower 95% indicator 6,016, the upper 95% indicator 7,424. In the main group, the average mathematical indicator of the detection duration of diastolic dysfunction of the left ventricle was mean 6,443±0,390, the lower 95% indicator was 5,678, the upper 95% indicator was 7,208.

In the control group, the average structural indicator of the duration of detection of diastolic dysfunction of the left ventricle was the median 8,000±0,314, the lower 95% indicator was 7,384, the upper 95% indicator was 8,616. In the main group, the average structural indicator of the duration of detection of diastolic dysfunction of the left ventricle was the median 4,000±0,106, the lower 95% indicator was 3,792, and the upper 95% indicator was 4,208. There was no statistical accuracy difference between the groups (px2=0,947). Graph 7 shows the results.

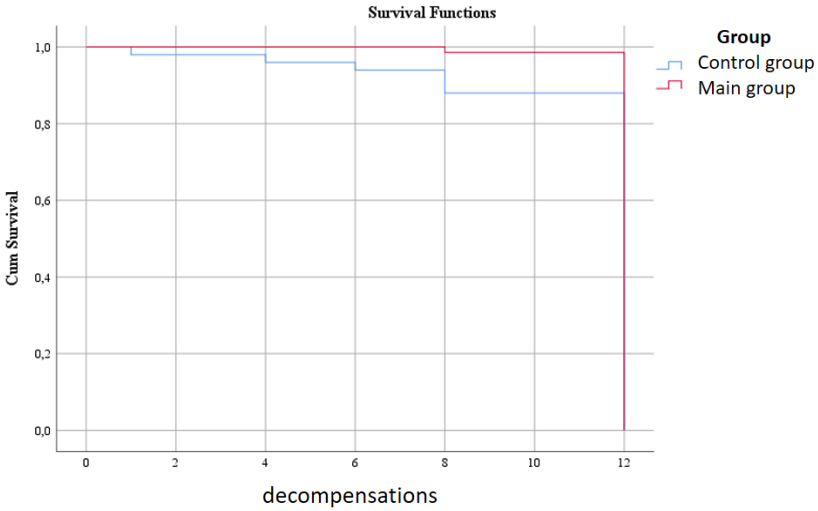


Graph 7. Detection of left ventricular diastolic dysfunction

Among the patients included in our research, the average mathematical indicator of the duration of detection of decompensations in the control group was the mean 11.260±0.314, the lower 95% indicator was 10.644, the upper 95% indicator was

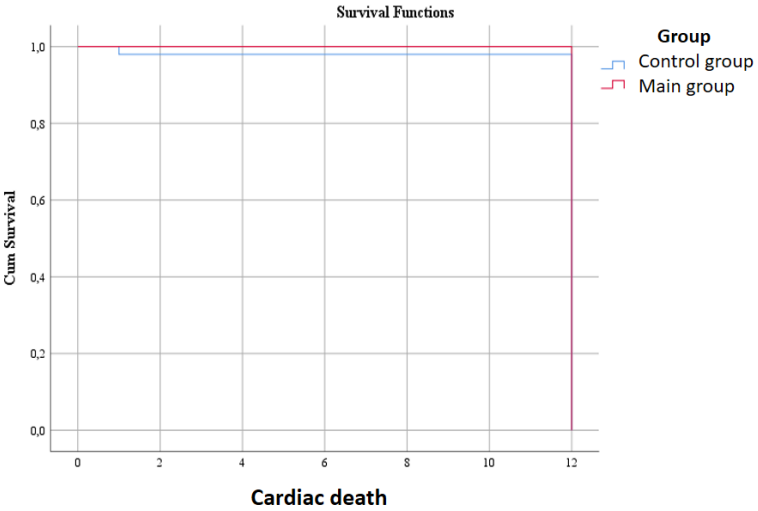
11.876. In the main group, the average mathematical indicator of the duration of detection of decompensations was the mean 11.943±0.057, the lower 95% indicator was 11.831, and the upper 95% indicator was 12.055. There was a statistically significant difference in the overall duration of detecting decompensations between the groups (p_x^2=0,014). The results are shown in Graph 8.

During the comparative analysis conducted using the Kaplan-Meier method, it was found that the duration of detection of the frequency of decompensation in patients was on average (11,260±0,314) in the control group, and 11,943±0,057 in the main group.



Graph 8. Detection of decompensations

During the 12-month observation period of the cardiotoxic effects of anti-cancer CDT on survival indicators, there was no significant difference between the study groups (p=0,237). A graphical representation of the obtained results is shown in Graph 9.



Graph 9. Detection of cardiac death

RESULTS

1. After the 4th course of anti-cancer CDT , 40 (57.1%) of the patients included in the main group developed preserved fractional heart failure (pW<0.001). After the 8th course of anti-cancer CDT, 4,2% of patients included in the main group developed heart failure with a mildly reduced ejection fraction, and 66,6% developed heart failure with preserved ejection fraction (pW=0,317). [1,3,4,6,8-13,17].
2. Immediately after the end of anti-cancer CDT, the average index of left ventricular ejection fraction was 47 (52,7±0,6%) of patients in the control group and 62 (55,1±0,5%) of patients in the main group decreased compared to the basal values. During the comparative analyzes of the results between the

groups, a statistical accuracy difference was obtained (pu=0.001). [15, 20].

3. One year after anti-cancer CDT, patients in the main group showed relatively weak development in left ventricular structural and functional disorders (LVSV, LVDD, LVEF) compared to the control group. A statistically significant difference was observed between the research groups (p<0,001, p<0,001, p<0,001). [14,17].
4. Among patients who did not undergo cardiology examinations during the inter-course period after one year of CDT, 36% developed heart failure with preserved ejection fraction, 54,0% developed heart failure with mildly reduced ejection fraction, and 10,0% developed heart failure with reduced ejection fraction. Among patients who underwent cardiology examinations during the inter-course period, 74,3% developed heart failure with preserved ejection fraction, 12,9% developed heart failure with mildly reduced ejection fraction, and no patients developed heart failure with reduced ejection fraction. There was a statistically significant difference observed between the research groups (p_u<0,001). [14,17,18].
5. During the 12-month observation period, the detection time of the occurrence of decompensation cases in patients was on average (11,260±0,314) in the control group, and (11,943±0,057) in the main group. A statistically significant difference was observed between the research groups (p=0,014). [16,19].
6. During the analysis of the life indicators due to anti-cancer CDT during the 12-month observation period, no statistically significant difference was observed between the research groups (p=0,237). [16,19].

PRACTİCAL RECOMMENDATİONS

1. Regular use of TTE in early diagnosis of the heart failure component of developing cardiotoxicity in low-risk breast cancer patients treated with definite cardiotoxic combination chemotherapy, 4th, 8th, and 1 year post-treatment LVEF should be kept under control.
2. An increase in NT-proBNP, even at very low levels, should be considered as a high-risk indicator in the early diagnosis of preserved heart failure in patients with breast cancer undergoing CDT combined with Anthracyclines. It should be checked on the 4th, 8th of the treatment course, after the end of the treatment and 1 year later.
3. As a result of timely diagnosis in a center with a cardio-oncology team with an organized approach in the medical plan, the necessary treatment and prophylactic measures can be carried out in these patients at the early stage of heart failure, thereby preventing death due to the treatment aimed at the main disease or the incomplete discontinuation of the anti-cancer treatment, it may be possible to reduce the percentage both disability and death and increase survival.

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LIST OF ABBREVIATIONS

AC/TC	– Adriamycin, cyclophosphamide/ taxane, cyclophosphamide
ACE	– angiotensin converting enzyme
ACE inhibitor	– angiotensin converting enzyme inhibitor
HfrEF	– heart failure with reduced ejection fraction
ESC	– European Society of Cardiology
AntiHER2	– anti-Human epidermal growth factor receptor 2
Anti-VEGF	– anti-Vascular endothelial growth factor
ARB	– angiotensin II receptor blocker
ARNI	– angiotensin receptor/neprilysin inhibitor
BB	– Beta Blocker
BNP	– B-type Natriuretic Peptide
CAF(FAC)	– 5-fluorouracil, adriamycin, cyclophosphamid
Echo	– echocardiography
ECG	– electrocardiography
HER-2	– Human epidermal growth factor receptor 2
HFA	– Heart Failure Association
CDT	– Chemotherapy
MRB	– mineralocorticoid receptor blocker
MPO	– Myeloperoxidase
NT-proBNP	– N-terminal pro B-type natriuretic peptide
PASP	– pulmonary artery systolic pressure
EDV	– end-diastolic volume
LAEDVI	– left atrium end-diastolic volume index
LVEF	– left ventricular ejection fraction
LVDV	– left ventricular diastolic volume
LVDD	– left ventricular diastolic dysfunction
LVSD	– left ventricular systolic dysfunction
LVSI	– left ventricular systolic index
LVSV	–left ventricular stroke volume
ESV	– end systolic volume
FEC	– 5-fluorouracil, epirubicin, cyclophosphamide
QLS	–global longitudinal strain

LAVI	– left atrial volume index
TAC	–Docetaxel (Taxotere), Adriamycin, Cyclophosphamide
T-DM1	– trastuzumab-emtansine
TRV	– tricuspid regurgitation velocity
TTE-	– Transthoracic echocardiography

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