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RESULTS OF A SINGLE-CENTER PROSPECTIVE OBSERVATIONAL STUDY: HOW TO TAKE CARE OF THE HEART OF A CANCER PATIENT

<i>Aim</i>	Search for subclinical manifestations of cardiotoxicity in cancer patients at high and very high risk of cardiotoxicity and evaluation of the effectiveness of drug primary prevention during the antitumor treatment.
<i>Material and methods</i>	The study included 150 cancer patients with a high and very high Mayo Clinic (USA) Cardiotoxicity Risk Score. The main group consisted of 84 patients at high and very high risk of cardiotoxicity who were prescribed cardioprotective therapy, including a fixed combination of the angiotensin-converting enzyme inhibitor (ACEI) perindopril and the beta-blocker bisoprolol with trimetazidine. The comparison group consisted of 66 patients who refused cardioprotective drugs or had intolerance to them. All patients underwent 24-hour ambulatory blood pressure monitoring (ABPM) and multibiomarker analysis, including measurements of troponin I (TnI), N-terminal pro-brain natriuretic peptide (NT-proBNP), myeloperoxidase (MPO), soluble tumor suppressor type 2 (sST2), and two-dimensional echocardiography (EchoCG) with assessment of left ventricular global longitudinal systolic strain (LV GLS) before chemotherapy and 1, 3, 6, 9, and 12 months after the start of cardiotoxic antitumor therapy.
<i>Results</i>	In patients of the comparison group already at 6 months, the left atrial volume index (LAVI) was significantly increased, and the left ventricular end-diastolic volume index (LVEDVi) showed a tendency towards an increase reaching a significant difference by 9 months of observation. In the main group, these parameters did not significantly change during the study. At the last stage of observation, there were statistically significant differences in LAVI and LVEDVi between the compared groups. The dynamics of LV GLS in the compared groups showed multidirectional changes. In the main group, this parameter remained virtually unchanged while in the comparison group, it decreased by $\geq 15\%$ in 13 patients and reached a statistically significant difference. Clinically pronounced cardiotoxicity and a decrease in the left ventricular ejection fraction (LVEF) developed in 7 of these patients. During the antitumor treatment, the concentrations of the biomarkers remained within the reference values, with the exception of Tn I. The greatest differences between the groups were noted in the analysis of mortality. Thus, by the final visit, 13.1% of patients had died in the main group while in the comparison group, mortality was almost two times higher and reached 22.7%.
<i>Conclusion</i>	The study demonstrated clinical effectiveness of the cardioprotective therapy in cancer patients at high and very high risk of cardiotoxicity. The patients who did not receive the primary drug prevention of cardiovascular toxicity had a statistically significant impairment of the LV systolic function, an increased number of developed complications, and a higher mortality.
<i>Keywords</i>	Cardiotoxicity; left ventricular global longitudinal systolic strain; cardioprotection; cardiovascular toxicity; left ventricular ejection fraction
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Antitumor therapy has made a significant contribution to increasing the survival and life expectancy of cancer patients. Recently, there has been a progressive increase in the number of patients in stable remission due to the timely and effective use of antitumor treatment [1–3]. However, treatment with

cytostatic drugs can cause various manifestations of cardiotoxicity and death from it in about a third of patients [4,5]. Previously, cardiotoxicity was considered to be a decrease in left ventricular ejection fraction (LVEF) that occurred during or after anticancer treatment [6].

Studies of the toxicity of chemo, targeted and immune therapy in recent years indicate that as a result of the treatment of malignant neoplasm (MN), in addition to systolic and/or diastolic myocardial dysfunction, such cardiovascular complications (CVD) as coronary heart disease (CHD), arterial hypertension (AH), strokes, endo-, myo-, and/or pericarditis, cardiac rhythm and conduction disturbances, thrombosis, and bleeding [1, 2, 7–9].

In this regard, cardiovascular toxicity is one of the leading causes of death in cancer patients, unrelated to the course of the oncological process [10].

The occurrence of such complications adversely affects the course of the underlying disease and the quality of life of patients, including due to the forced discontinuation of effective antitumor therapy regimens and an increase in the duration of course treatment.

The staff of the Mayo Clinic (USA) described the “multiple injury hypothesis”, according to which two components affect the risk of cardiotoxic complications: the planned treatment regimen, due to the involvement of various molecular pathways of antitumor drugs metabolism, and the general somatic status of the patient [11].

In accordance with the recommendations of the European Society of Cardiology (ESC) 2022, before starting antitumor treatment, all patients should be stratified into risk groups in accordance with the upcoming treat-

ment regimen, the presence of classical risk factors and comorbid cardiovascular pathology, and patients from the high and very high risk groups should be prescribed cardio-protective therapy. This strategy helps to prevent and timely detect cardiotoxicity in the early stages of its occurrence [12].

Currently, criteria for subclinical cardiotoxicity have been identified. In case of asymptomatic complications, medical correction is also required, and, if necessary, a timely revision of the antitumor therapy regimen.

To detect subclinical cardiotoxicity in all patients, a detailed analysis of complaints and medical history, a thorough physical examination, subsequent long-term follow-up and comprehensive clinical, instrumental, and laboratory examination are necessary throughout the entire treatment period and after its completion [11–17].

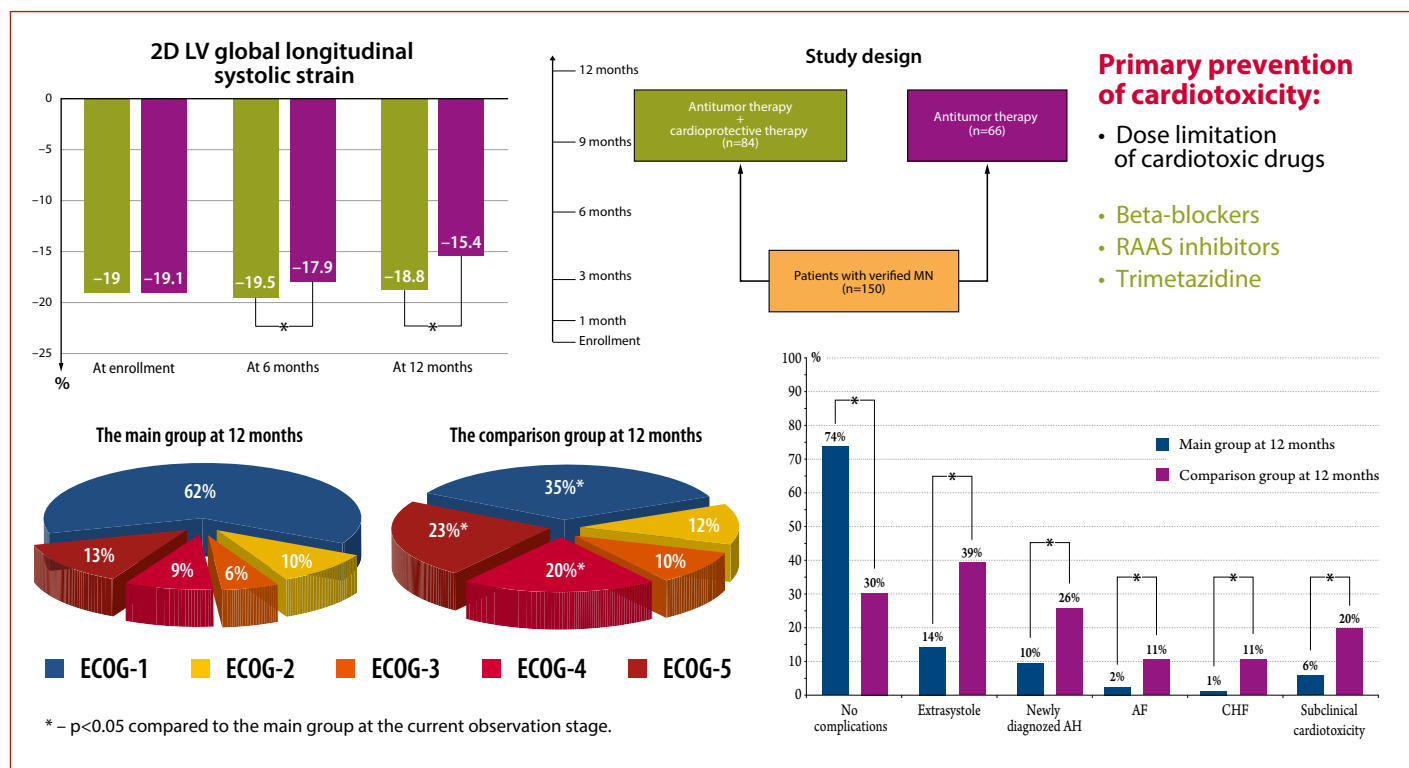
The aim of the study

The aim of the study: search for subclinical manifestations of cardiotoxicity in cancer patients with high and very high risk of cardiotoxicity, as well as to evaluate the effectiveness of its primary drug prevention in the process of antitumor treatment.

Material and methods

A prospective observational study was conducted from March 2021 to December 2023. 150 patients

Central illustration. Results of a single-center prospective observational study:
How to take care of the heart of a cancer patient



with verified malignant neoplasm who were prescribed cardiotoxic antitumor treatment were included. All patients signed an informed voluntary consent to participate in the study, which was approved by the Interuniversity Ethics Committee (Protocol No. 03–21 dated 03/18/2021).

The criteria for inclusion in the study were morphologically verified cancer, prescribed cardiotoxic antitumor treatment, high or very high risk of cardiotoxicity according to the Mayo Clinic scale (USA), since ESC guidelines on cardioncology were published only in 2022, assessment of the patient's clinical and functional condition according to the ECOG scale (Eastern Cooperative Oncology Group) from 0 to about 3 points, signed informed voluntary consent of the patient to be included in the study.

Criteria for non-inclusion: permanent atrial fibrillation, severe liver and kidney damage, metastases in the central nervous system, uncontrolled hypertension, intolerance to angiotensin converting enzyme inhibitors (iACE) or beta-blockers, ECOG score of 4 points, patient's refusal to participate in the study. The study also did not include cancer patients and those receiving antitumor therapy who had recently suffered acute cardiovascular complications (acute cerebrovascular accident, acute myocardial infarction that occurred within 12 months prior to inclusion) in the anamnesis.

The risk of cardiotoxicity was assessed using a scoring system proposed by the Mayo Clinic specialists [11, 13, 14]. Depending on the prescribed treatment regimen, as well as the presence of risk factors and/or cardiovascular diseases in the patient, before starting antitumor treatment, the risk level of cardiotoxicity in patients was determined, calculated by the sum of the points (Table 1).

Preventive cardioprotective therapy in the form of a fixed combination of ACE inhibitors perindopril and beta-blocker bisoprolol is recommended for all patients; the myocardial cytoprotector trimetazidine is additionally prescribed to patients at very high risk of cardiotoxicity with coronary heart disease. Dur-

ing the study, a comparison group (n=66) was formed, which included patients with intolerance to iACE, beta-blockers and/or trimetazidine or who refused to take these drugs. The most common complications were dry cough, bradycardia, allergic reactions, and hyperkalemia. The main group consisted of patients (n=84) with a high and very high risk of cardiotoxicity who agreed to additionally take these cardioprotective drugs.

Statins were not prescribed to patients, as ESC guidelines for their use as primary prevention of cardiotoxicity were published in 2022, when patient recruitment and follow-up were almost completed. Patients who had previously been prescribed statins continued taking them.

Statins were not prescribed to newly enrolled patients on the recommendation of oncologists due to the fear of a potential increase in the activity of liver enzymes, the level of which could also increase as a result of chemotherapy.

The comparative characteristics of the main and comparison groups of patients are presented in Table 2. The groups were comparable in all characteristics, except for the statistically significantly more frequently detected history of myocardial infarction in the patients of the main group.

When included in the study, most patients took antihypertensive drugs irregularly or sporadically.

Despite this, an analysis of concomitant medication use in the study groups revealed some differences. For example, patients in the control group were statistically significantly more likely to take potassium-sparing diuretics, loop diuretics, and alpha-blockers (Table 3).

The groups also did not differ in the localization and stage of the tumor process. The majority were patients with breast cancer (56%), colorectal cancer (12.7%) and lung cancer (8.7%).

The most cardiotoxic antitumor drugs that patients received were anthracyclines [18] and trastuzumab. The patients of the compared groups did not differ in the frequency of prescribing cardiotoxic antitumor drugs. Patients in the main group received higher total doses of doxorubi-

Table 1. Assessment of the risk of cardiotoxicity before antitumor therapy

The risk associated with the planned treatment		Patient-related risk
High risk – 4 points	Anthracyclines, cyclophosphamide, clofarabine, herceptin	Each of the listed factors is 1 point: cardiomegaly or chronic heart failure; coronary artery disease/equivalent (peripheral artery disease); hypertension; diabetes; history of anthracycline treatment; previous or combined radiation therapy for the chest; age <15 or >65 years; female
Intermediate risk – 2 points	Docetaxel, pertuzumab, sunitib, sorafenib	
Low risk – 1 point	Bevacizumab, dasatinib, imatinib, lapatinib	
Absence of risk – 0 points	Etoposide, rituximab, thalidomide	

The total calculated risk of cardiotoxicity is determined by the sum of the scores corresponding to each risk factor: >6 – very high, 5–6 – high, 3–4 – intermediate, 1–2 – low, 0 – very low. Adapted from [7].

Table 2. Comparative characteristics cancer patients included in the study

Parameter		The main group (n=84)	Comparison group (n=66)
Age, years		59.9±11.7	61.1±12.3
Risk of cardiotoxicity, n (%)	high	40 (47.6)	33 (50.0)
	very high	44 (52.4)	33 (50.0)
Gender, n (%)	male	15 (17.9)	12 (18.2)
	female	69 (82.1)	54 (81.8)
Arterial hypertension, n (%)		71 (84.5)	51 (77.3)
Obesity, n (%)		22 (26.2)	19 (28.8)
Diabetes, n (%)		13 (15.5)	19 (26.0)
CAD, n (%)		51 (60.7)	33 (50.0)
History of myocardial infarction, n (%)		9 (10.7)	2 (3.0)*
Chronic heart failure, n (%)		28 (33.3)	27 (40.9)
Cancer stage, n (%)	I	6 (7.1)	4 (6.1)
	II	49 (58.3)	40 (60.6)
	III	24 (28.6)	17 (25.7)
	IV	5 (5.9)	5 (7.6)

*p<0.05 compared to the main group. AH, arterial hypertension; CAD, coronary artery disease; MI, myocardial infarction; DM, diabetes mellitus; CHF, chronic heart failure.

cin – 246.3 (240–240) mg/m² compared with patients in the comparison group – 210 (180–240) mg/m², taking into account all courses of treatment.

According to current data, Trastuzumab has dose-independent cardiotoxicity, and therefore its average dose received by patients has not been evaluated.

All patients underwent a clinical and instrumental examination upon inclusion in the study, as well as 1, 3, 6, 9 and 12 months after the start of chemo and/or targeted therapy. The examination of each patient included the collection of complaints, medical history, physical examination, electrocardiography, daily blood pressure monitoring, two-dimensional echocardiography using Speckle tracking technology and assessment of the global longitudinal strain of the left ventricle.

Cardiotoxicity was defined as a decrease in LVEF by 10% or more from baseline or to a level of <50%, or with a decrease in LV strain ≥15% compared with baseline data with preserved LVEF.

Statistical processing of the obtained research data was carried out using the Statistica Base program, version 12 (StatSoft Russia). The differences in the analyzed parameters were considered statistically significant at p<0.05.

The Kolmogorov–Smirnov and Shapiro–Wilk criteria were used to assess the correspondence of quantitative parameters to the normal distribution. The comparison of quantitative variables obeying a normal distribution was carried out using parametric methods.

Table 3. Concomitant drug therapy in cancer atients included in the study

Medicament	The main group (n=84)	Comparison group (n=66)
Thiazide diuretics	14 (16.7)	6 (9.1)
Potassium-sparing diuretics	10 (11.9)	24 (36.4)*
Loop diuretics	12 (14.3)	18 (27.3)*
Alpha blockers	3 (3.6)	9 (13.6)*
Morphine	13 (15.5)	14 (21.2)

Data are presented as n (%).

*p<0.05 compared to the main group.

For the analysis of categorical variables, the x-square criterion was used to test the hypothesis of differences between the compared groups. The Student's t criterion was used to compare the values of data groups in order to determine the validity of the differences. The criterion was applied for ordinal variables Wilcoxon–Mann–Whitney for comparing two independent samples, as well as the criterion Kruskal–Wallis method for comparing medians of independent groups, followed by the application of Fisher's exact test for data analysis in conjugacy tables.

Results

When assessing the volume parameters of the heart chambers during antitumor treatment, a statistically significant positive effect of cardioprotective therapy was noted (Table 4).

Thus, during echocardiography in patients of the main group, the indexed volume of the left and right atrium, as well as the indexed end systolic volume and indexed end diastolic volume of the left ventricle did not significantly change statistically throughout the 12-month follow-up. At the same time, after 6 months of follow-up, the indexed volume of the left atrium increased statistically significantly in patients in the comparison group, and these differences persisted throughout the entire follow-up period.

In addition, in the comparison group, throughout the entire follow-up period, there was a tendency to increase the indexed LV end-diastolic volume, which reached statistically significant differences, both with its initial value and with this indicator at the 9-month follow-up stage in the main group. The dynamics of the indexed LV end-systolic systolic volume in the comparison group had a similar trend and reached statistically significant differences with the initial values by the final stage of follow-up.

The listed volumetric changes in all chambers of the heart indicate their remodeling, which can be inter-

Table 4. Dynamics of echocardiographic parameters in cancer patients during 12-month follow-up

Parameter	Group	Baseline	After 1 month of follow-up	After 3 months of follow-up	After 6 months of follow-up	After 9 months of follow-up	After 12 months of follow-up
Indexed volume of the left atrium, ml/m ²	main	32.4±9.4	32.9±9.3	33.1±9.5	32.6±8.2	32.2±9.4	32.1±10.5
	comparison	32.1±8.7	33.2±8.7	34.2±9.8	36.9±10.1 ^{*,**}	38.2±9.5 ^{*,**}	37.8±9.3 ^{*,**}
Indexed end-diastolic volume, ml/m ²	main	57.3±10.2	57.7±10.7	57.9±11.5	56.9±10.8	55.2±9.3 [*]	55.4±9.4 [*]
	comparison	54.8±13.2	56.1±11.7	57.9±11.5	58.2±12.4 [*]	59.3±14.2 ^{*,**}	64.8±19.2 ^{*,**}
Indexed end systolic volume, ml/m ²	main	22.2±5.5	22.4±5.9	22.0±5.2	22.3±4.5	21.9±4.7	21.8±4.6
	comparison	22.6±10.9	23.9±9.1	24.7±9.8	24.2±5.7	24.5±11.3	25.6±11.8 ^{*,**}
LVEF, %	main	60.7±4.7	60.6±4.9	61.3±4.2	61.4±4.4	61.7±3.6	61.8±3.8
	comparison	61.7±7.2	59.3±6.6	58.8±7.5	57.9±5.1	56.3±9.4 ^{*,**}	57.2±8.9 ^{*,**}
LV GLS, %	main	-19.0±2.5	-19.3±2.1	-19.5±2.2	-19.5±2.1	-19.6±2.5	-18.8±6.4
	comparison	-19.1±3.6	-18.6±3.4	-18.3±3.3 ^{*,**}	-17.9±3.4 ^{*,**}	-17.4±4.0 ^{*,**}	-15.4±8.0 ^{*,**}
Indexed LV myocardial mass, g/m ²	main	M	107.4±25.1	104.7±15.7	103.3±12.9	101.7±23.6 [*]	99.6±27.6 [*]
		F	91.7±21.9	92.0±20.2	87.7±20.3	85.9±17.1	84.2±15.1 [*]
	comparison	M	99.6±26.2	105.4±33.3	102.9±36.7	111.3±26.5 [*]	107.3±26 ^{*,**}
		F	87.5±24.5	88.1±25.4	93.6±22.2	93.1±16.9	105.0±20.4 ^{*,**}
Indexed right atrium volume, ml/m ²	main	24.6±7.1	24.1±6.3	24.1±6.6	24.3±6.7	23.1±6.0	22.9±6.2
	comparison	24.8±8.4	25.5±8.9	26.3±9.5	27.4±9.7	28.6±8.8 ^{*,**}	29.5±8.8 ^{*,**}

*p<0.05 compared to the enrollment visit; **p<0.05 compared to the main group at the same observation stage. LV EF, left ventricular ejection fraction; LV GLS, left ventricular global longitudinal strain.

preted as one of the manifestations of subclinical cardiotoxicity.

The change in LVEF in the compared groups had a similar trend. In the patients of the main group, there was only a tendency to increase this indicator. At the same time, in the LVEF group, there was a significant decrease in LVEF by the 9th month of follow-up. At the same time, after 12 months of follow-up, not only its further decrease was revealed, but also statistically significant differences in this indicator with patients in the main group. However, the absolute value of this indicator remained within the normal range.

The dynamics of global longitudinal strain LV GLS as one of the most sensitive markers of cardiotoxicity in the compared groups was multidirectional. So, in the main group, the indicator practically did not change throughout the entire observation period.

LV GLS absolute decrease of ≥15%, which is associated with subclinical cardiotoxicity, was observed in 5 (5.9%) patients in the main group. One of them showed a decrease in LVEF of <50%, however, during the observation and dose adjustment of cardioprotective treatment, as well as after changing the antitumor therapy regimen, the contractility of the myocardium was restored.

In the comparison group, a decrease in LV GLS ≥15% from baseline was detected in 13 (19.7%) patients and acquired statistically significant differences (p<0.05) with the main group. Clinically pronounced cardiotoxicity and decreased LVEF developed in 7 of these 13 patients.

The correction of their antitumor treatment regimen did not lead to the restoration of myocardial contractility.

The dynamics of indexed left ventricular myocardial mass also reached statistically significant differences between the groups by the 9th month of follow-up and persisted until the final visit.

According to some authors, an increase in LV myocardial mass in cancer patients after chemotherapy is also a manifestation of its cardiotoxicity [19].

When analyzing the main indicators of daily blood pressure monitoring before the start of antitumor therapy in the compared groups, lower blood pressure levels in the comparison group were noted. However, during the long-term observation, their multidirectional dynamics were noted. So, in the main group, all indicators of daily blood pressure monitoring decreased statistically significantly, and in the comparison group they increased statistically significantly, reaching maximum values by the final visit (Table 5).

It should be noted that in the main group of patients who additionally received cardio and vasoprotective therapy, the number of patients with dipper daily blood pressure increased 2.2-fold by the end of follow-up, and those with the most unfavorable nightpeaker daily blood pressure decreased 3.2-fold compared with those at the stage of inclusion in the study.

The opposite dynamics was noted in the patients of the comparison group.

When assessing the level of biomarkers of damage (troponin I), fibrosis (type 2 soluble tumorigenic-

Table 5. Data from daily blood pressure monitoring in cancer patients during 12-month follow-up

BP, mm Hg		Baseline	After 1 month of follow-up	After 3 months of follow-up	After 6 months of follow-up	After 9 months of follow-up	After 12 months of follow-up
24-h SBP	Main group	133.5±17.9	122.6±14.9	121.1±15.7	118.3±12.4	118.1±11.7	118.5±13.7*
	Comparison group	120.8±14.8**	123.1±17.3	117.9±12.5	124.2±17.1	123.5±15.1	138.6±13.9*,**
24-h DBP	Main group	80.5±9.9	74.3±9.8*	72.2±9.9*	71.1±7.6*	69.4±7.6*	70.4±8.5*
	Comparison group	74.7±8.9**	74.4±10.7	72.3±9.4	77.1±11.3**	76.0±10.7**	87.6±9.1*,**
Daytime SBP	Main group	135.1±16.8	123.3±17.5*	122.9±16.5*	119.6±11.3*	121.8±12.3*	120.6±16.8*
	Comparison group	121.6±12.8**	124.5±19.5	117.4±14.9	123.3±18.8	125.5±17.9**	135.9±11.1*,**
Daytime DBP	Main group	82.1±9.7	75.9±9.9*	73.9±9.7*	72.5±7.5*	70.6±8.3*	72.5±8.6*
	Comparison group	77.8±8.3**	76.1±11.3	72.7±9.5	76.8±12.3	75.3±9.9**	86.9±10.1*,**
Nighttime SBP	Main group	129.6±21.8	117.6±17.2*	115.2±16.5*	113.7±12.2*	112.8±10.9*	113.6±14.1*
	Comparison group	119.8±24.7**	118.1±19.5	123.3±18.7**	127.7±11.9	127.0±11.8*,**	134.6±23.2*,**
Nighttime DBP	Main group	76.8±11.8	70.2±9.9*	67.6±7.7*	68.3±7.6*	65.6±8.4*	66.1±8.8*
	Comparison group	71.6±11.6**	71.9±12.5	68.2±10.9	75.7±19.8**	71.4±14.5	82.1±12.6*,**

*p<0.05 compared to the enrollment visit; **p<0.05 compared to the main group at the same observation stage.
BP, blood pressure; SBP, systolic BP; DBP, diastolic BP.

ty suppressor – sST2), myocardial dysfunction (N-terminal fragment of the brain natriuretic peptide – NT proBNP) and oxidative stress (myeloperoxidase – MPO) in the main group, only a downward trend was noted during the 12-month follow-up (Table 6).

On the contrary, in the comparison group, there was a tendency to increase these enzyme immunoassays, but it reached statistically significant differences from the baseline value only when assessing the level of NTproBNP.

The level of sST2 in the patients of the main group tended to decrease during follow-up, remaining within the normal range, while in the patients of the comparison group it increased.

The absolute value of other analyzed biomarkers, with the exception of troponin I, remained within the normal range during antitumor treatment of cancer patients from high and very high risk groups of cardiotoxicity.

When assessing the clinical and functional status of patients before the start of antitumor therapy according to the criteria of the Eastern Cooperative Oncology Group (ECOG), statistically significant differences were

not found between the compared groups. At 12 months of follow-up in the main group of ECOG-1 patients, no statistically significant changes in the clinical condition were found, only a tendency to a slight decrease in their number was noted.

At the same time, in the comparison group among ECOG-1 patients who did not receive cardioprotective therapy, a statistically significant decrease in their number was noted after 1 month of antitumor treatment. In the course of further follow-up of patients in this group, a progressive and statistically significant decrease in their number was revealed, which reached a practical threefold decrease in the 9th and 12th months of follow-up.

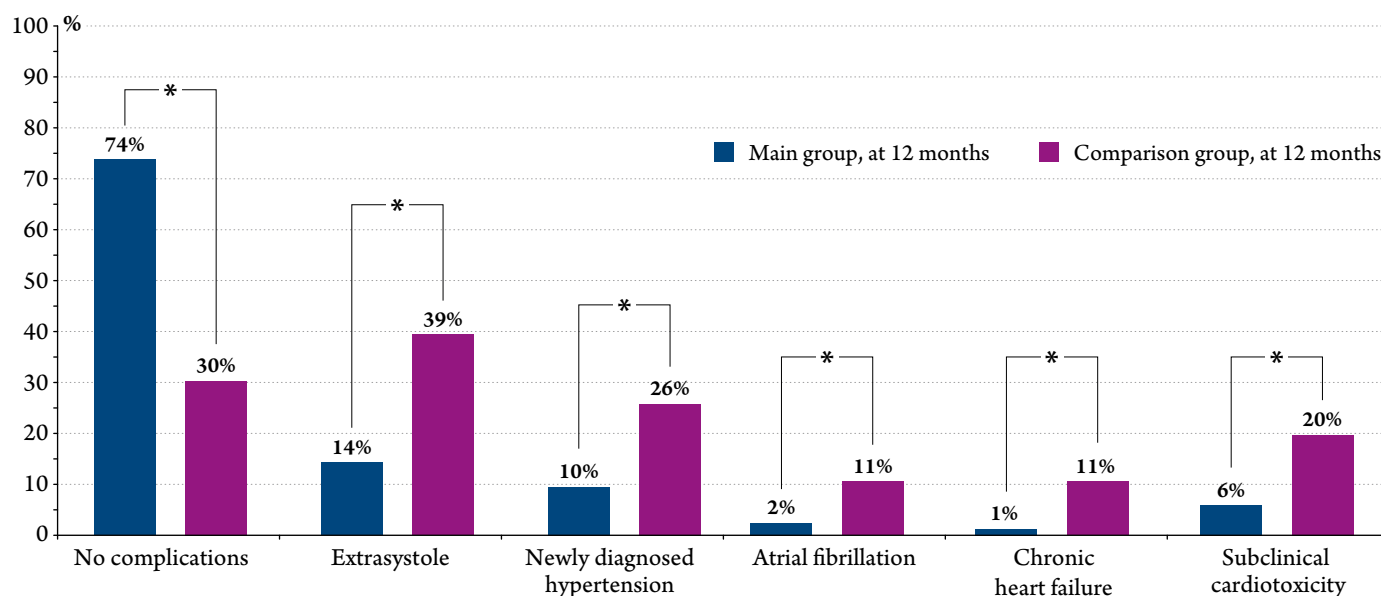
When included in the study, there were no patients in the compared groups who needed to stay in bed all day and needed constant care (ECOG-4). However, after a month of antitumor therapy in the comparison group (without cardioprotection), the number of such patients reached 7%. At the same time, at all subsequent stages of treatment, every fifth patient in this group

Table 6. Dynamics of biomarkers of cardiotoxicity in cancer patients during follow-up

Biomarker of myocardial damage and fibrosis		At enrollment	After 6 months of follow-up	After 12 months of follow-up
ng/ml (normal range<0.48-1.0)	Main group	1.63 (0.8–2.2)	1.59 (1.0–1.8)	1.48 (0.75–1.8)
	Comparison group	1.37 (0.7–1.7)	2.0 (0.9–2.1)	1.4 (0.6–2.4)
pmol/ml (normal range<125)	Main group	17.5 (5.9–18.3)	16.9 (4.8–22.9)	15.8 (5.3–20.3)
	Comparison group	32.6 (7.5–35.3)**	25.5 (5.7–39.3)	52.8 (5.5–77.9)*,**
MPO, ng/ml (normal range 8-239)	Main group	35.6 (6.0–41.6)	20.5 (4.0–27.8)	10.4 (2.95–13.05)*
	Comparison group	23.7 (9.1–34.8)	21.3 (5.6–30.3)	21.3 (13.9–28.3)
ng/ml (normal range 7.1-49.3)	Main group	22.5 (3.9–31.1)	15.9 (3.8–16.3)	11.2 (4.55–13.0)
	Comparison group	35.1 (6.1–57.7)**	38.2 (7.95–57.35)**	35.9 (7.9–64.7)**

*p<0.05 compared to the enrollment visit; **p<0.05 compared to the main group at the same observation stage. TnI, troponin I; NT-proBNP, N-terminal pro-B-type natriuretic peptide; MPO, myeloperoxidase; sST2, soluble suppression of tumorigenicity type 2.

Figure 1. Incidence of cardio- and vasotoxic complications of antitumor therapy in cancer patients during 12-month follow-up



* $p < 0.05$ compared to the main group

lost the ability to self-care and continued treatment in the palliative care unit. In the main group, the number of patients who were bedridden and unable to self-care was 2 times less than in the comparison group.

The most significant differences between the groups were noted in the analysis of mortality. Thus, by the final visit, 13.1% of patients in the group of patients receiving cardioprotective therapy had died, while in the patients in the comparison group, mortality reached 22.7% ($p = 0.04$).

When analyzing the incidence of cardiovascular complications of antitumor treatment as manifestations of cardio- and vasotoxicity, their occurrence was noted in 26.2% of patients in the main group, while in the comparison group – in 69.7%, i.e. almost 2.5 times more often (Fig. 1). At the same time, heart failure or LV systolic dysfunction in patients without cardioprotection was observed 8 times more often, atrial fibrillation – 4.4 times, a decrease in LV GLS $\geq 15\%$ – 3.3 times, extrasystole – 2.8 times, newly diagnosed hypertension – 2.7 times, and venous thrombosis of the lower extremities – 2.5 times more often than in patients receiving primary drug prophylaxis of cardio and vasotoxicity of antitumor therapy.

Thus, it can be stated that cardioprotection with cardiovascular drugs in cancer patients receiving cardiotoxic chemo and/or targeted therapy slowed down myocardial remodeling and effectively prevented the development of clinically significant cardiovascular complications induced by antitumor treatment, and statistically significantly reduced overall mortality.

Discussion

In accordance with the 2022 ESC Guidelines on Cardio-Oncology, all cancer patients should have a comprehensive assessment of their somatic status and a basic stratification of the risk of developing cardiotoxic complications before, during, and after antitumor treatment [12]. After the end of antitumor therapy, a clinical and instrumental examination of the cardiovascular system should be repeated, and further tactics for monitoring and preventing cardio and vasotoxicity should be determined [2, 20].

To assess the systolic function of the myocardium during the treatment of a patient with cardiotoxic cytotoxic agents, the most widespread use of LVEF is two-dimensional echocardiography. However, its high intra- and inter-study variability is currently shown. It is also known that in a number of patients, a decrease in LVEF is detected in the long-term follow-up period, only after the onset of clinical manifestations of cardiotoxicity, when complete restoration of myocardial contractility is difficult even with timely initiation of drug correction of systolic dysfunction. The use of new, highly sensitive technologies such as speckle tracking with LV GLS detection helps to cope with this problem [11, 21–23].

The study clearly demonstrated the occurrence of clinically significant cardiovascular complications described in the literature in cancer patients on the background of chemo- and targeted therapy [10, 12, 13]. The results obtained confirm the effectiveness of cardioprotective therapy in cancer patients with high and very high risk of cardiotoxicity. The appointment of a fixed combination of iACE, beta-blockers in combination

with trimetazidine before the start of antitumor treatment can positively affect the functional state of the cardiovascular system, improving LV systolic function and overall well-being of cancer patients.

Studies conducted in the last decade provide data on the diagnostic capabilities of biomarkers of damage, fibrosis, myocardial dysfunction, and oxidative stress in the early detection of subclinical cardiotoxicity. However, the information available in the literature on enzyme immunoassay parameters of cardiotoxicity of antitumor treatment is not unambiguous, often contradictory, and requires further study and clarification [19, 24–27].

The ambiguity of the literature data on the need to monitor the level of these biomarkers in patients who are prescribed cardiotoxic treatment for cancer was confirmed in our study. Thus, when assessing the level of troponin I during a 12-month follow-up, no statistically significant changes were found in patients of both groups. At the same time, there was a tendency to a transient increase in this indicator in patients of the comparison group by the 6th month of observation.

The level of NT-proBNP in the main group remained virtually unchanged during the 12-month follow-up, whereas in the comparison group it increased significantly by the final visit.

When analyzing the MPO level during antitumor treatment, a decrease was noted in patients in the main group, which reached statistically significant differences at the final visit compared with the inclusion visit. At the same time, there was no statistically significant dynamics of this indicator of oxidative stress in the comparison group.

The ST2 level in the main group initially turned out to be lower than in the patients of the comparison group, and its further decrease against the background of cardioprotective therapy reached statistically significant differences by the end of the follow-up. In the comparison group, this indicator of myocardial fibrosis remained virtually unchanged throughout the study.

Thus, it can be stated that during the primary drug prophylaxis of iACE cardiotoxicity, beta-adrenoblocker in combination with myocardial cytoprotector, during antitumor treatment, the level of biomarkers of myocardial damage did not increase, and the concentration of biomarkers of inflammation and myocardial fibrosis decreased statistically significantly.

The results of our study allow us to share the point of view of many authors, according to which determining the level of circulating biomarkers in cancer patients has a prognostic value and allows us to determine the cardiotoxicity of antitumor therapy at the subclinical level [24–27]. However, the lack of a standardized methodology does not yet allow us to determine the exact way they are used in clinical practice and include them in appropriate diagnostic algorithms [28–32].

Conclusion

After the completion of antitumor therapy, we identified statistically significant differences in the clinical and functional status of patients, which was assessed on the ECOG scale. These data were fully correlated with the dynamics of the assessed indicators.

The most important result of this study is a twofold reduction in the annual mortality of cancer patients who, along with antitumor treatment, received primary drug prophylaxis of cardio- and vasotoxicity induced by antitumor therapy (13.1 and 22.7% respectively).

The results obtained confirm the important role and clinical effectiveness of cardioprotective therapy with a combination of iACE, beta-blocker and myocardial cytoprotector trimetazidine, which was previously noted in the agreed opinion of Russian experts on the prevention, diagnosis and treatment of cardiovascular toxicity of antitumor therapy [33]. At the same time, timely determination of LV GLS makes it possible to detect myocardial dysfunction long before clinical manifestations of cardiotoxicity, and subsequent primary drug prophylaxis in cancer patients receiving antitumor therapy improves their clinical and functional condition and prognosis during and after cancer treatment.

Early detection of signs of cardiotoxicity is crucial for improving the quality of life and long-term prognosis of survival in cancer patients.

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Conflict of interest

Authors declare no conflict of interest.

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