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Heart remodeling in patients with severe systolic dysfunction due tocancer chemotherapy

Objective	Comparative analysis of structural and functional specific features of the heart in patients with toxic cardiomyopathy (TCMP) with a low left ventricular ejection fraction (LVEF) and severe, chronic heart failure (CHF) and in patients with idiopathic dilated cardiomyopathy (DCMP) and similar LVEF and CHF severity.
Materials and Methods	This observational, single-site study included 15 patients with TCMP (12 of them received treatment including anthracycline antibiotics and 3 patients received targeted therapies) and 26 patients with idiopathic DCMP. Data of echocardiography were compared for patients with TCMP and DCMP with comparably low LVEF of <40%.
Results	In patients with severe heart damage associated with antitumor therapy with low LVEF, volumetric and linear indexes of left and right ventricles and the left atrium (left atrial volume index (LAVI), 33.7 (21.5–36.9) ml/m^2; right ventricular end-diastolic dimension (RVDd), 2.49 (1.77–3.53) cm; and end-diastolic volume index (EDVI), 78.0 (58.7–90.0) ml/m^2) were considerably less than in the DCMP group (LAVI, 67.1 (51.1–85.0) ml/m^2; RVDd, 4.05 (3.6–4.4) cm; and EDVI, 117.85 (100.6–138.5) ml/m^2, p<0.0001). Furthermore, LV wall thickness and pulmonary artery systolic pressure did not differ in these groups. Both in men and women with TCMP, LAVI and EDVI were significantly less than in men and women with DCMP.
Conclusion	The study showed significant differences in parameters of cardiac remodeling. In TCMP patients as distinct from DCMP patients, despite a pronounced decrease in LVEF, LV dilatation was absent or LV volumetric parameters were moderately increased with a more severe somatic status.

Keywords	Cardiac remodeling; cardiotoxicity; antitumor therapy; anthracycline antibiotics
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The development of new cancer treatments has significantly increased the life expectancy of cancer patients. However, the administration of drugs within anticancer regimens, such as anthracyclines, trastuzumab, and other HER2 (human epidermal growth factor) receptor antagonists, antimetabolites, alkylating agents, tyrosine kinase inhibitors (TKI), angiogenesis inhibitors, is associated with the risk of cardiac toxicity [1].

There is a wide variety of adverse cardiovascular effects of oncology drugs, but the term cardiac toxicity is not yet conclusively defined. Most modern definitions in manuals and clinical trials are focused on reduced left ventricular ejection fraction (LVEF) during or after anticancer treatment and on the development of the clinical picture of heart failure (HF) [2]. There is a sufficient number of works on cardiac complications of anticancer therapy [3, 4]. In 2016, a new position paper by European cardiologists on monitoring cardiac toxicity during anticancer treatment was presented at the annual congress of the European Society of Cardiology (ESC) [5].

According to this document, cardiovascular complications of cancer treatment can be classified into these main categories: myocardial dysfunction and HF, coronary artery disease (CAD), valvular disease, abnormal cardiac rhythm and conduction (primarily related with drugs inducing QT prolongation), hypertension, thromboembolic complications, peripheral vascular disease, stroke, pulmonary hypertension, and pericardial diseases. Anthracycline (doxorubicin) cardiac toxicity is the most well studied.

In addition, each effective new anticancer drug is associated with possible adverse cardiovascular effects.

For example, in 2012, a new class of drugs (checkpoint inhibitors) was approved, which are monoclonal antibodies that target cytotoxic T-lymphocytes binding the PD-1, PD–L1, and CTLA4 receptors. These medicines are a key to the implementation of the anticancer immune response and tumor escape from immunosurveillance [6]. Their effectiveness in the treatment of many disseminated forms of malignant tumors, such as melanoma, lung cancer, and lymphomas, has been demonstrated. However, checkpoint inhibitors are associated with the risk of fulminant myocarditis, mainly as part of combined treatment regimens [6].

Awareness of the importance of controlling cardiac toxicity arising from the treatment of oncological diseases has resulted in the opening of cardio-oncology clinics in wealthy countries [7, 8]. Their task is screening and treatment, where applicable, of short- and long-term complications of chemoradiation therapy after the completion of a round of polychemotherapy.

The guidelines published by respected facilities experienced in the treatment of such patients are not national or international. These are, rather, the experience of specific teams. Mayo Clinic has proposed the most interesting instrument, a model for risk assessment, monitoring, and management of patients undergoing chemotherapy [9].

Notable is a certain paradox: On the one hand, it is widely known that cardiotoxic complications can be extremely severe, with the development of cardiomyopathy accompanied by a decrease in systolic function (LVEF <40%), functional class FC III–IV congestive heart failure (CHF) resulting in death. On the other hand, these are quite rare (up to 10% in the case of doxorubicin) [10, 11]. Lenneman et al. performed a retrospective analysis of the period from 1987 to 2011. A total of 51,312 heart transplantations was carried out due to terminal stages of CHF; of these, 453 (0.88%) patients fit the definition of adriamycin cardiomyopathy [12].

Due to a low rate of events, the relevant studies use soft endpoints, such as drug effects on the levels of troponin, N-terminal pro-brain natriuretic peptide (NTproBNP), et cetera [13].

Despite the increasing number of relevant clinical studies, the pattern of myocardial remodeling and its regenerative potential after the administration of anticancer therapy during progressive growth remain understudied, and anticancer drug-related cardiomyopathy is considered by many authors to be dilated cardiomyopathy (DCMP) [14, 15]. It is now believed that early cardiac toxicity is associated with the development of DCMP with reduced LV mass and wall thickness. It is thought that patients who were affected in childhood can have restrictive cardiomyopathy. Late-onset chronic progressive cardiac toxicity is characterized by cardiac dysfunction following a latent period of 1 or more years after completion of anthracycline-based treatment. This type of cardiac toxicity has an asymptomatic period; it can be followed by the development of chronic DCMP with restriction or restrictive cardiomyopathy with the subsequent development of CHF [16].

The objective of the study was to perform a comparative analysis of structural and functional characteristics of the heart in patients with toxic cardiomyopathy (TCMP) with low LVEF and severe CHF and patients with idiopathic DCMP with similar LVEF and severity of CHF.

Materials and methods

Over a 15 year period, Hospital Therapy Department No. 2 (Medical Faculty of N.I. Pirogov Russian National Research Medical University at the premises of City Clinical Hospitals No. 12 and No. 24) examined more than 200 patients with lymphomas who underwent chemoradiation regimens including anthracyclines; 216 patients with chronic lymphocytic leukemia; and 97 patients with chronic myelogenous leukemia.

The study design was observational. All patients signed informed consent to be examined and treated.

Severe cardiac toxicity with CHF and decreased (<40%) LVEF was diagnosed in 10 patients treated with anthracyclines under chemoradiation regimens and one patient with chronic myelogenous leukemia during the administration of nilotinib. We also observed two patients with breast cancer treated with doxorubicin (and trastuzumab), a patient with lung cancer who received pembrolizumab, and a patient suffering from chronic lymphocytic leukemia and TCMP, which developed when obinutuzumab was used together with ibrutinib (Table 1). All patients underwent clinical examination, electrocardiography, and echocardiography using an ultrasound scanner AcusonSequia 512 (USA). Acute-onset chronic progressive cardiac toxicity was detected in three patients, late-onset chronic progressive cardiac toxicity in eight patients, and long-term cardiac toxicity in four patients. In nine patients, LVEF <30% was identified; six patients had LVEF varying from 31% to 38.5%.

Echocardiographic indicators of patients with TCMP and 26 patients with idiopathic DCMP with similar decreased LVEF (control group) were compared. Patients with alcoholism, diabetes mellitus (DM), or hypertension were excluded from the control group. A subgroup of patients with idiopathic DCMP underwent coronary angiography and myocardial perfusion imaging. The control group did not include female patients with periportal cardiomyopathy. The age of patients in the

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Table 1. Anamnestic data of patients with TCMP

No.	Age	Sex	Diagnosis	Drug	Premorbid	Outcome	HF FC	Duration of HF, months
1	54	Female	HL	Anthr.	Healthy	Alive, effective treatment	III	48
2	48	Male	NHL	Anthr.	Spongiform cardiomyopathy	Alive, effective treatment	III	24
3	65	Female	NHL	Anthr.	VES	Alive, effective treatment	III	24
4	21	Male	HL	Anthr.	Healthy	Alive, effective treatment	III	132
5	61	Male	CML	Nil.	Healthy	Alive, effective treatment	II	36
6	47	Female	BC + ALL	Anthr. + RT	Healthy	Alive, effective treatment	III	120
7	58	Female	NHL	Anthr.	Healthy	Alive, effective treatment	II	12
8	24	Male	HL	Anthr.	Healthy	Unknown	III	48
9	74	Male	CLL	Ibr. + Obin.	AF	Died of pneumonia	III	0.25
10	49	Female	HL	Anthr.	Healthy	Died	III	12
11	35	Female	HL	Anthr.	Healthy	Died	III	120
12	40	Female	HL	Anthr.	Healthy	Died	III	72
13	43	Female	NHL	Anthr.	Healthy	Died	III	36
14	65	Female	BC	Anthr. + Trast.	Healthy	Died	III	24
15	77	Male	LC	Pembr.	Healthy	Alive, effective treatment	III	6

Anthr., anthracyclines; Ibr., ibrutinib; Obin., obinutuzumab; Nil., nilotinib; Pembr., pembrolizumab; Trast., trastuzumab;
F, female; M, male; FC, functional class; HF, heart failure; CML, chronic myelogenous leukemia; CLL, chronic lympocytic leukemia;
HL, Hodgkin's lymphoma; NHL, non-Hodgkin's lymphoma; ALL, acute lymphoblastic leukemia;
BC, breast cancer; RT, radiation therapy; VES, ventricular extrasystoles; AF, atrial fibrillation.

study groups did not differ (Table 2). The data of patients with TCMP and DCMP are presented before treatment or at the beginning of treatment. In 17 patients with DCMP, LVEF <30% was identified, and nine patients had LVEF varying from 31% to 37%. It should be noted that there were significantly more females among patients undergoing regimens that included doxorubicin (apparently, due to higher sensitivity to doxorubicin). In comparison, there were more male patients in the control group with DCMP (Table 2). Sinus rhythm prevailed in both study groups, p=0.32. No data on FC and duration of CHF were available for seven patients with DCMP.

Table 2. Clinical and demographic characteristics in the study groups

Parameter	TCMP, n=15	DCMP, n=26	p
Age (years)	49.0 (40.0–65.0)	48.5 (44.0–55.0)	0.72
Female, n (%)	9 (60)	10 (38.5)	0.18
Male, n (%)	6 (40)	16 (61.5)	
FC (II/III/IV), n	2/13/0; 15	4/13/2; 19	0.33
Duration of CHF (months)	36.0 (12.0–72.0)	24.0 (9.0–72.0)	0.92

TCMP, toxic cardiomyopathy; DCMP, dilated cardiomyopathy;
LVEF, left ventricular ejection fraction; CHF, chronic heart failure.

Statistical analysis. The Mann-Whitney methods were used to compare two independent variables, and the Wilcoxon test was used to compare two dependent samples. The Pearson's chi-squared test was used to evaluate relative indicators (rates and proportions). All data were presented as the median and interquartile range and 95% confidence interval (95% CI) or absolute numbers and percentages. Given a small sample of the examined patients, the level of statistical significance p<0.005 was adopted.

Results and Discussion

Table 3 shows echocardiographic indicators of each patient with a severely damaged heart after the administration of anticancer drugs. The table shows that despite decreased LVEF, patients have slightly increased or not increased end-diastolic volume (EDV), end-systolic volume (ESV), left atrial volume index (LAVI), and linear echocardiographic indicators.

The comparison of TCMP and DCMP patients with comparable decreased LVEF revealed no significant

Table 3. Echocardiographic indicators of each patient with TCMP and severely damaged heart after the administration of anticancer drugs

No.	Sex	Drug	LVEF, %	LAVI, mL/m²	LV EDV, mL	LV ESV, mL	PASP, mmHg
1	Female	Anthr.	28.0	45	98	70.6	47
2	Female	Anthr.	22.5	23.7	134.9	104.5	40.9
3	Female	Anthr.	28.4	30.6	161.6	115.7	50
4	Female	Anthr.	31.5	21.5	92.9	63.6	22.8
5	Female	Anthr.	24.6	19.5	144.2	108.7	59.3
6	Female	Anthr.	33.4	33.7	101.1	67.3	65
7	Female	Anthr. + Trast.	15.3	33.8	83.3	70.5	29.7
8	Female	Anthr.	22.9	40.1	131.4	101.3	55
9	Female	Anthr.	18.0	46.0	180.0	147.6	60
10	Male	Ibr. + Obin.	30.3	36.9	165.9	107.6	25
11	Male	Anthr.	38.5	34.9	184.4	113.4	35
12	Male	Anthr.	37.2	16.7	125	78.5	51.2
13	Male	Anthr.	24.5	24.8	124.4	93.9	30
14	Male	Nil.	26.4	13.9	165.5	121.8	71
15	Male	Pembr.	35.0	35.5	168.0	109.0	43

LVEF (%) – n>55; LAVI (mL/m²) – n: 16–28; LV EDV (mL) – F: 56–104; M: 67–155; LV ESV (mL) – F: 19–59; M: 22–58; PASP, mmHg – n<30; F, female; M, male; Ibr., ibrutinib; Nil., nilotinib; Obin., obinutuzumab; Pembr., pembrolizumab; Trast., trastuzumab; LAVI, left atrial volume index; EDV, end-diastolic volume; ESV, end-systolic volume; LVEF, left ventricular ejection fraction; PASP, pulmonary artery systolic pressure.

Table 4. Comparative characteristics of linear and volume indicators of heart function in patients with TCMP and DCMP with decreased LVEF

Groups/indicators	TCMP, n=15	DCMP, n=26	p
HR, bpm	98 (94.0–122.0), 95% CI: 86.4–109.6	86.0 (63.0–100.0), 95% CI: 72.0–100.0	0.006
LVEF, %	28.0 (22.9–33.4), 95% CI: 23.7–32.3	25.5 (24.0–32.0), 95% CI: 21.6–29.5	0.82
LA (cm)	3.99 (3.6–4.7), 95% CI: 3.5–4.5	4.9 (4.5–5.3), 95% CI: 4.4–5.4	0.0006
LAVI, mL/m²	33.7 (21.47–36.9), 95% CI: 27.4–40.0	67.1 (51.1–85.0), 95% CI: 47.5–86.7	< 0.0001
RAEDD, cm	2.49 (1.77–3.53), 95% CI: 1.8–3.2	4.05 (3.6–4.4), 95% CI: 3.6–4.5	0.0001
LVEDD, cm	5.59 (5.2–6.0), 95% CI: 5.3–5.9	6.6 (6.1–6.9), 95% CI: 6.1–7.1	< 0.0001
EDVI, mL/m²	78.0 (58.7–90.0), 95% CI: 65.9–90.1	117.85 (100.6–138.5), 95% CI: 102.2–133.5	< 0.0001
ESVI, mL/m²	55.7 (36.8–66.2), 95% CI: 46.6–64.8	88.4 (73.4–95.2), 95% CI: 74.8–102.0	< 0.0001
PASP, mmHg	47.0 (30.0–59.3), 95% CI: 37.5–56.5	45.5 (36.4–52.0), 95% CI: 38.3–52.7	0.93
IVS, cm	0.9 (0.72–1.04), 95% CI: 0.75–1.05	0.97 (0.9–1.1), 95% CI: 0.82–1.12	0.16

TCMP, toxic cardiomyopathy; DCMP, dilated cardiomyopathy; HR, heart rate; LVEF, left ventricular ejection fraction; LAD, left atrial diameter; LAVI, left atrial volume index; RAEDD, right atrial end-diastolic dimension; LAEDD, left atrial end-diastolic dimension; EDVI, end-diastolic volume index; ESVI, end-systolic volume index; PASP, pulmonary artery systolic pressure; IWT, interventricular septal wall thickness; IVS, intact ventricular septum.

Table 5. LAVI, EDV, and LVEF depending on duration of CHF

Parameter	TCMP, n = 15	p	DCMP, n = 19	p
LAVI, mL/m², CHF < 24 months	34.9 (30.6–36.9)	0.14	63.4 (40.2–85.0)	0.33
LAVI, mL/m², CHF > 24 months	23.1 (18.1–36.9)		68.1 (61.4–96.6)	
EDV, mL/m², CHF < 24 months	85.6 (78.0–96.5)	0.13	100.0 (95.0–121.3)	0.1
EDV, mL/m², CHF > 24 months	66.3 (54.9–81.9)		123.5 (106.1–142.5)	
LVEF, %, CHF < 24 months	28.4 (18.0–35.0)	0.77	26.5 (25.0–32.0)	0.97
LVEF, %, CHF > 24 months	27.2 (24.6–32.5)		25.0 (24.5–33.0)	

TCMP < 24 months – n = 7; TCMP > 24 months – n = 8; DCMP < 24 months – n = 10; DCMP > 24 months – n = 10. LAVI, left atrial volume index; EDV, end-diastolic volume; LVEF, left ventricular ejection fraction; CHF, chronic heart failure; DCMP, dilated cardiomyopathy; TCMP, toxic cardiomyopathy.

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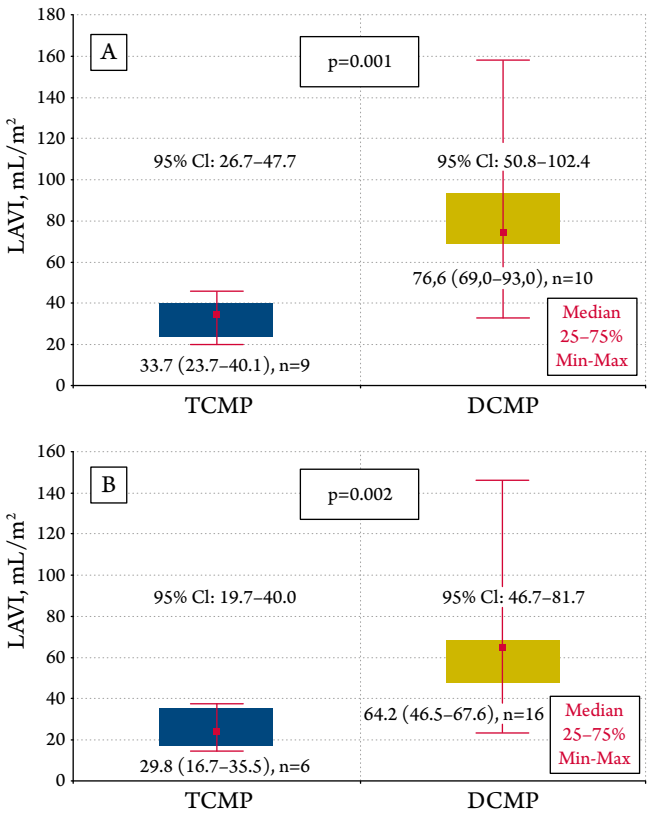
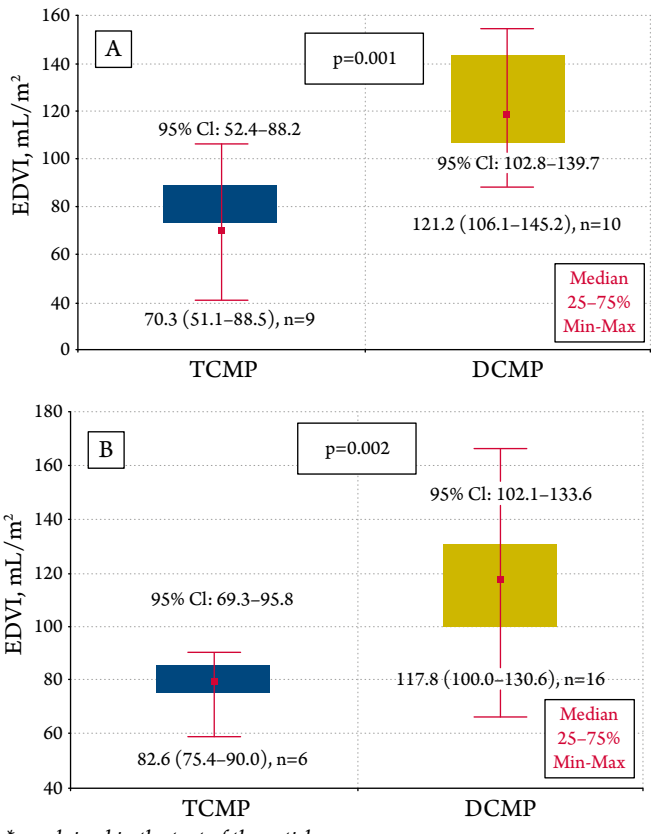
Figure 1. Left atrial volume index in the TCMP and DCMP groups, in female (A) and male (B) patients*



*, *explained in the text of the article.*

Figure 2. EDVI in the TCMP and DCMP groups in female (A) and male (B) patients*



*, *explained in the text of the article.*

differences in these indicators (Table 4). Table 4 shows that volume and linear indicators of the LV, right ventricle (RV), and left atrium (LA) are significantly lower in patients with severely damaged hearts with decreased LVEF during the treatment with anticancer drugs than in the DCMP group. The LV wall thickness and pulmonary artery systolic pressure (PASP) do not differ between the groups.

The sex-specific analysis showed that heart rate in female patients with TCMP (103.0 (98.0–122.0) bpm) is higher than in those with DCMP (71.5 (62.0–86.0) bpm), p=0.004; male patients with TCMP and DCMP had similar HR: 96.0 (93.0–191.5) and 86.0 (69.0–119.3) bpm, p=0.33.

As mentioned above, the study included three male patients with acute-onset chronic non-anthracycline cardiac toxicity caused by the administration of obinutuzumab, nilotinib, and pembrolizumab. Patients with non-anthracycline TCMP were statistically insignificantly younger (74.0 [61.0–77.0] years old) than three male patients with anthracycline TCMP (24.0 [24.7–48.0] years old) resulting from the treatment of lymphomas (p=0.08). The indicators studied were similar: wall thickness did not differ, volume indicators varied insignificantly: LAVI 24.8 (16.7–34.9) and 35.5 (13.9–36.9) mL/m² (p=0.66), LV EDVI 75.4 (36.8–57.0) and 90.0 (85.6–96.5) mL/m² (p=0.08) in patients with anthracycline and non-anthracycline TCMP, respectively.

The echocardiographic indicators studied were compared within subgroups of female (Figures 1A and 2A) and male patients (Figures 1B and 2B). Figures 1 and 2 show that in total and in both male and female subgroups, LAVI and EDVI were significantly lower in the TCMP group than in DCMP patients.

We also studied structural and functional indicators of the heart in patients with TCMP and DCMP according to the duration of CHF (median 24 months).

Table 5 shows that volume indicators are statistically insignificantly lower in patients with TCMP and duration of CHF more than 24 months than in TCMP patients with duration of CHF less than 24 months, and are lower with similar LVEF. Notably, among patients with TCMP with a longer duration of CHF, some patients underwent radiation treatment of the mediastinum with restrictive processes in the myocardium [17]. These trends were different in patients with DCMP.

Patients with severe TCMP were treated from the first clinical encounter to date following the standard CHF therapy: ACE inhibitors, beta-blockers, diuretics, cardiac glycosides [18]. Our patients with TCMP generally had low baseline blood pressure, which required very slow titration of ACE inhibitors and beta-blockers and

Figure 3. LVEF indicators before and after treatment of CHF

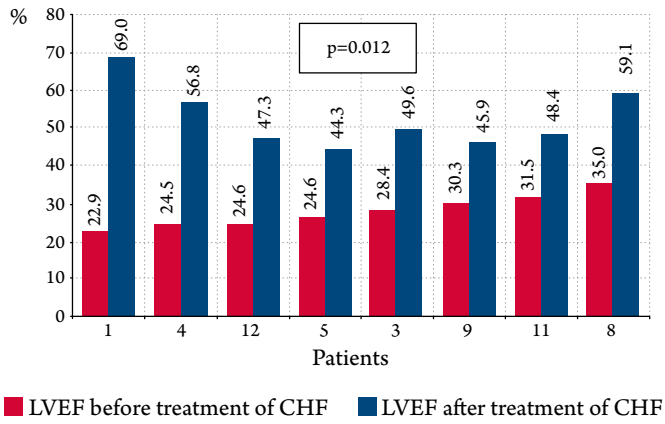
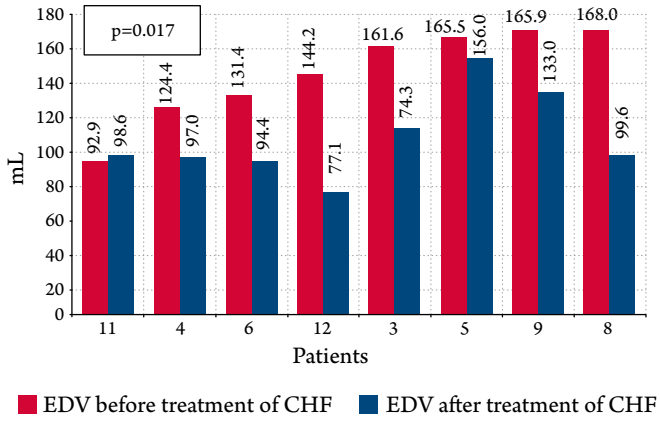


Figure 4. EDV indicators before and after treatment of CHF



limited the use of diuretics. During treatment, there was an increase in LVEF and improvement of clinical status (LVEF before treatment 27.4 [24.55–30.9] % and after treatment 49.0 [46.6–57.5] %, p <0.012, n=8). The follow-up period was 6 months. Figure 3 shows that LVEF increased to the values corresponding to intermediate or close to normal [18]. In some cases, we observed the normalization of this indicator. Despite the absence of the baseline increase of EDV or its moderate increase resulting from the anticancer therapy, the decrease was observed after the effective treatment of CHF, except in one case with a moderate increase (Figure 4): patient Z., 35 years old, with extremely severe TCMP and LVEF 31.5% before treatment. This may also be explained by the presence of restrictive processes in the myocardium of patients with TCMP [19].

Discussion

Orthotopic heart transplantation or the use of an artificial ventricle is an effective treatment method for severe CHF with low LVEF of any origin [20]. Oliveira et al. present cases of «dramatic» increase of LVEF in patients with TCMP during resynchronizing therapy. They underline, however, that the study was conducted in a smaller number of subjects. We demonstrated that this effect is also achieved with the timely administration of optimal drug treatment.

Unfortunately, a rather large proportion of our patients, including those who had a significant increase in LVEF, died after rapid deterioration (n=6). This was most often the case with patients residing in other places, when they were lost to follow-up. This suggests that such patients require continuous monitoring of their status for timely heart transplantation in case of deterioration. Possibly they should be included on a surgical waitlist.

It was shown retrospectively that patients with HF resulting from chemotherapy have outcomes when modern methods of CHF treatment are used, including resynchronization therapy, artificial ventricle, and heart transplantation; outcomes that are similar to outcomes with other forms of HF. There were almost no cases of cancer recurrence after orthotopic heart transplantation in patients with TCMP [20].

In 2016, the ESC working group on myocardial and pericardial diseases proposed creation of a new category, hypokinetic nondilated cardiomyopathy [21]. It represents the disease course options antecedent to the development of DCMP and is characterized by diffuse LV hypokinesis without dilation. However, a moderate reduction of LVEF (<45%) is also observed in such cases. The reduced systolic function without significant dilation of the heart chambers was instantly identified in patients with TCMP presented in our work.

Heart remodeling in TCMP resembles changes in acute severe myocarditis, with acute reduction of LVEF, normal sizes and volume of the heart chambers, and increased wall thickness associated with the presence of secondary edema [22]. At the same time, we observed neither large dilation of the cavities nor progressive reduction of LVEF in distant and late-onset TCMP with a longer duration of CHF.

Thus, we demonstrated distinct structural and functional indicators of the myocardium in patients with severe TCMP as compared to patients with idiopathic DCMP with similarly low LVEF. This was the first time it was shown that remodeling of the heart in acute-onset toxic cardiomyopathy is largely different from remodeling in DCMP. It should also be said that patients with TCMP had more severe somatic status than patients with DCMP and similar LVEF.

Our study is limited by a small number of observations. This suggests that it is necessary to create registers of patients receiving treatment with cardiotoxic agents, especially anthracyclines.

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Conclusions

1. Volume and linear indicators for the left and right ventricles and the left atrium were significantly lower In patients with a heart severely damaged during the administration of anticancer drugs and low LVEF than in those with DCMP. The left ventricular wall thickness and pulmonary artery systolic pressure did not differ between the groups.
2. These differences were similar in male and female patients.
3. This type of heart remodeling resembles remodeling in severe acute myocarditis.
4. Timely optimal drug therapy for CHF in severe patients with TCMP leads to the rapid improvement of clinical status and a corresponding increase in left ventricular ejection fraction.

List of Abbreviations

Anthr., anthracyclines. DCMP, dilated cardiomyopathy. F, female. VES, ventricular extrasystoles. Ibr., ibrutinib. LVESVI, left ventricular end-systolic volume index. LVESVI, left ventricular end-systolic volume index. LAVI, left atrial volume index. TCMP, toxic cardiomyopathy. EDV, end-diastolic volume. ESV, end-systolic volume. RT, radiation therapy. HL, Hodgkin's lymphoma. M, male Nilo., nilotinib. NHL, non-Hodgkin's lymphoma. ALL, acute lymphoblastic leukemia. Pembr., pembrolizumab. BC, breast cancer. PASP, pulmonary artery systolic pressure. PWT, LV posterior wall thickness. IWT, interventricular septal wall thickness. Trast., trastuzumab. CLL, chronic lymphocytic leukemia. CML, chronic myelocytic leukemia. LAD, left atrial diameter. ESC, European Society of Cardiology. NTproBNP, N-terminal pro-brain natriuretic peptide. TKI, tyrosine kinase inhibitors.

No conflict of interest is reported.

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REFERENCES

1. Markman TM, Markman M. Cardio-Oncology: mechanisms of cardiovascular toxicity. F1000Research. 2018;7:113. DOI: 10.12688/f1000research.12598.1
2. Perez IE, Taveras Alam S, Hernandez GA, Sancassani R. Cancer Therapy-Related Cardiac Dysfunction: An Overview for the Clinician. Clinical Medicine Insights: Cardiology. 2019;13:117954681986644. DOI: 10.1177/1179546819866445
3. Lenneman CG, Sawyer DB. Cardio-Oncology: An Update on Cardiotoxicity of Cancer-Related Treatment. Circulation Research. 2016;118(6):1008–20. DOI: 10.1161/CIRCRESAHA.115.303633
4. Ballard W, Vader J. Prevention of Cardiotoxicity in the Cancer Patient. Current Cardiovascular Risk Reports. 2017;11(11): 31. DOI: 10.1007/s12170-017-0558-1
5. Zamorano JL, Lancellotti P, Rodriguez Muñoz D, Aboyans V, Asteggiano R, Galderisi M et al. 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC). European Heart Journal. 2016;37(36):2768–801. DOI: 10.1093/eurheartj/ehw211
6. Varricchi G, Galdiero MR, Marone G, Criscuolo G, Triassi M, Bonaduce D et al. Cardiotoxicity of immune checkpoint inhibitors. ESMO Open. 2017;2(4):e000247. DOI: 10.1136/esmoopen-2017-000247
7. Snipelisky D, Park JY, Lerman A, Mulvagh S, Lin G, Pereira N et al. How to Develop a Cardio-Oncology Clinic. Heart Failure Clinics. 2017;13(2):347–59. DOI: 10.1016/j.hfc.2016.12.011
8. Herrmann J, Loprinzi C, Ruddy K. Building a Cardio-Onco-Hematology Program. Current Oncology Reports. 2018;20(10): 81. DOI: 10.1007/s11912-018-0725-7
9. Larsen CM, Mulvagh SL. Cardio-oncology: what you need to know now for clinical practice and echocardiography. Echo Research and Practice. 2017;4(1):R33–41. DOI: 10.1530/ERP-17-0013
10. Takami Y, Hoshino N, Kato Y, Sakurai Y, Amano K, Higuchi Y et al. Recovery from anthracycline-induced cardiomyopathy with biventricular assist and valve repairs: A case report and literature review. The International Journal of Artificial Organs. 2018;41(7): 413–7. DOI: 10.1177/0391398818772497
11. Murtagh G, Lyons T, O'Connell E, Ballot J, Geraghty L, Fennelly D et al. Late cardiac effects of chemotherapy in breast cancer survivors treated with adjuvant doxorubicin: 10-year follow-up. Breast Cancer Research and Treatment. 2016;156(3): 501–6. DOI: 10.1007/s10549-016-3781-4
12. Lenneman AJ, Wang L, Wigger M, Frangoul H, Harrell FE, Silverstein C et al. Heart Transplant Survival Outcomes for Adriamycin-Dilated Cardiomyopathy. The American Journal of Cardiology. 2013;111(4): 609–12. DOI: 10.1016/j.amjcard.2012.10.048
13. Cardinale D, Ciceri F, Latini R, Franzosi MG, Sandri MT, Civelli M et al. Anthracycline-induced cardiotoxicity: A multicenter randomised trial comparing two strategies for guiding prevention with enalapril: The International CardioOncology Society-one trial. European Journal of Cancer. 2018;94:126–37. DOI: 10.1016/j.ejca.2018.02.005
14. Bozkurt B, Colvin M, Cook J, Cooper LT, Deswal A, Fonarow GC et al. Current Diagnostic and Treatment Strategies for Specific Dilated Cardiomyopathies: A Scientific Statement From the American Heart Association. Circulation. 2016;134(23):e579–646. DOI: 10.1161/CIR.0000000000000455
15. McGowan JV, Chung R, Maulik A, Piotrowska I, Walker JM, Yellon DM. Anthracycline Chemotherapy and Cardiotoxicity. Cardiovascular Drugs and Therapy. 2017;31(1):63–75. DOI: 10.1007/s10557-016-6711-0
16. Santos DS dos, Goldenberg RC dos S. Doxorubicin-Induced Cardiotoxicity: From Mechanisms to Development of Efficient Therapy. In: Cardiotoxicity Tan W, editor InTech;2018. [Av. at: https://www.intechopen.com/books/cardiotoxicity/doxorubicin-induced-cardiotoxicity-from-mechanisms-to-development-of-efficient-therapy. DOI: 10.5772/intechopen.79588]
17. Groarke JD, Nguyen PL, Nohria A, Ferrari R, Cheng S, Moslehi J. Cardiovascular complications of radiation therapy for thoracic malignancies: the role for non-invasive imaging for detection of cardiovascular disease. European Heart Journal. 2014;35(10):612–23. DOI: 10.1093/eurheartj/eht114
18. Mareev V.Yu., Fomin I.V., Ageev F.T., Begrambekova Yu.L., Vasyuk Yu.A., Garganeeva A.A. et al. Russian Heart Failure Society, Russian Society of Cardiology. Russian Scientific Medical Society of Internal Medicine Guidelines for Heart failure: chronic (CHF) and acute decompensated (ADHF). Diagnosis, prevention and treatment. Kardiologiia. 2018;58 (6S): 8–164. [Russian: Мареев В. Ю., Фомин И. В., Агеев Ф. Т., Беграмбекова Ю. Л., Васюк Ю. А., Гарганеева А. А. и др. Клинические рекомендации ОССН – РКО – РНМОТ. Сердечная недостаточность: хроническая (ХСН) и острая декомпенсированная

(ОДСН). Диагностика, профилактика и лечение. Кардиология. 2018;58(6S): 8-164]. DOI: 10.18087/cardio.2475
19. Nepomnyashchikh L.M., Lushnikova E.L., Klinnikova M.G., Molodykh O.P. Influence of doxorubicin on dilated myocardial remodeling during progressive growth. Siberian Medical Journal (Tomsk). 2011;26 (4–1):147–51. [Russian: Непомнящих Л. М., Лушникова Е. Л., Клинникова М. Г., Молодых О. П. Влияние доксорубицина на дилатационное ремоделирование миокарда в период прогрессивного роста. Сибирский медицинский журнал (Томск). 2011;26(4-1):147-51]
20. Oliveira GH, Qattan MY, Al-Kindi S, Park SJ. Advanced Heart Failure Therapies for Patients With Chemotherapy-Induced Cardiomyopathy. Circulation: Heart Failure. 2014;7(6):1050–8. DOI: 10.1161/CIRCHEARTFAILURE.114.001292
21. Pinto YM, Elliott PM, Arbustini E, Adler Y, Anastasakis A, Böhm M et al. Proposal for a revised definition of dilated cardiomyopathy, hypokinetic non-dilated cardiomyopathy, and its implications for clinical practice: a position statement of the ESC working group on myocardial and pericardial diseases. European Heart Journal. 2016;37(23):1850–8. DOI: 10.1093/eurheartj/ehv727
22. Kindermann I, Barth C, Mahfoud F, Ukena C, Lenski M, Yilmaz A et al. Update on Myocarditis. Journal of the American College of Cardiology. 2012;59(9):779–92. DOI: 10.1016/j.jacc.2011.09.074

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