Prus Yu. A., Ansheles A. A., Sergienko I. V.
National Medical Research Center of Cardiology, Moscow, Russia

Effects of cardioprotective tactics on the myocardial perfusion and contractile function of the left ventricular myocardium in cancer patients with evidence of doxorubicin-induced cardiotoxicity

Aim	To study the effect of cardioprotective tactics on parameters of left ventricular myocardial perfusion and contractility as per data from single-photon emission computed tomography in oncological patients with signs of anthracycline-induced cardiotoxicity.
Material and methods	The study included patients with oncological diseases (n=61) referred to polychemotherapy (PCT). For patients with signs of anthracycline-induced cardiotoxicity, a cardioprotective tactics was used, which included changing the PCT schedule and administering beta-blockers and angiotensin-converting enzyme inhibitors. For all patients at baseline, after the first four PCH courses, after initiation of the cardioprotective tactics and the next four PTC courses, the level of N-terminal pro-brain natriuretic peptide was measured and echocardiography and perfusion single-photon emission computed tomography were performed with assessment of left ventricular (LV) perfusion heterogeneity, systolic and diastolic function.
Results	Following four PTC courses, signs of cardiotoxicity were detected in 13 (21.3%) patients. On the background of the cardioprotective tactics, a further decrease in LV ejection fraction (EF) by –9±2% ($p<0.01$) was observed in 4 (30.8%) patients. In 9 (69.2%) patients, LV EF increased by 4±2% ($p<0.01$). Standard indexes of LV myocardial perfusion did not significantly change. In 7 patients, the cardioprotective tactics was associated with reduced severity of myocardial perfusion disorder, $LV\Delta\sigma T = -1.37\pm1.29$ ($p<0.05$), and in 4 patients, with reduced heterogeneity of myocardial perfusion, $LV\Delta\sigma H = -1.20\pm0.70$ ($p<0.05$).
Conclusion	The cardioprotective tactics prevents both further disorder of perfusion and decreases in parameters of left ventricular myocardial contractility in patients with anthracycline-induced cardiotoxicity.

Keywords	Cardio-oncology; polychemotherapy; doxorubicin; cardiotoxicity; myocardial perfusion; single-photon emission computed tomography
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Corresponding author Ansheles A. A. E-mail: a.ansheles@gmail.com

In the past few decades, diagnosis and treatment of cancer have improved progressively, substantially increasing the life expectancy at any age. However, anthracycline antibiotics remain the drugs of choice for patients with blood malignancies, soft tissue sarcomas, and solid tumors [1]. They are highly effective; however, their use is associated with cardiovascular toxicity that may include cardiovascular complications (CVCs), such as cardiomyopathy and heart failure (HF) [2]. The European Society for Medical Oncology Consensus defined cardiovascular toxicity criteria as a left ventricular ejection fraction (LVEF) drop > 10% of the baseline or LVEF drop<50% [3].

There is no standard effective therapy to prevent cardiovascular toxicity caused by anthracycline antibiotics. To this end and to treat CVCs during or after antitumor therapy, various groups of well-established drugs (such as beta-blockers and angiotensin-converting enzyme [ACE] inhibitors) are used; however, the evidence of their efficacy is conflicting. There are results of studies of their effects on preserving LV contractility using echocardiography. However, it is more important to study the effects of cardioprotective treatment on more delicate processes, such as LV myocardial perfusion, which can be evaluated using myocardial perfusion single-photon emission computed tomography (SPECT) synchronized with the electrocardiogram (C-SPECT).

Thus, our objective was to investigate the effects of cardioprotective treatment on LV perfusion and contractility parameters according to SPECT in cancer patients with signs of anthracycline-induced cardiovascular toxicity.

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Materials and methods

The study included patients of the Russian National Cardiology Research Center (n=61) diagnosed with cancer of various localization and various clinical stages who received adjuvant and neoadjuvant polychemotherapy (PCT). The work was carried out in the Laboratory of Atherosclerosis Phenotypes and the Department of Radionuclide Diagnostics and Positron Emission Tomography of the Russian National Cardiology Research Center. The patients were examined after signing informed consent. The ethics committee of the Russian National Cardiology Research Center approved the study protocol.

The study included patients with soft tissue sarcoma (42.62%), Ewing's sarcoma (13.11%), osteosarcoma (18.03%), breast cancer (8.20%), uterine leiomyosarcoma (6.56%), nasal cavity osteosarcoma (4.92%), esophageal sarcoma (1.64%), ovarian cancer (1.64%), and Hodgkin's lymphoma (3.28%).

The following PCT regimens were used in different combinations:

- HD AI – doxorubicin 60 mg/m^2+ifosfamide 2,000 mg/m^2 days 1–5+uromitexan 2,000 mg/m^2 days 1–3
- AI – doxorubicin 20 mg/m^2 days 1–3+ ifosfamide 2,500 mg/m^2 days 1–3
- AP – doxorubicin 90 mg/m^2 i/v 96 hour infusion+cisplatin 120 mg/m^2 day 1+filgrastim 5 μg/kg days 5–15
- VAI – vincristine 2 mg+doxorubicin 60 mg/m^2 day 1+ifosfamide 2,000 mg/m^2 days 1–5
- ADIC – dacarbazine 225 mg/m^2 days 1–4+doxorubicin 22.5 mg/m^2 days 1–4+filgrastim 300 μg days 5–14
- BEACOPP-14 – cyclophosphamide 650 mg/m^2 day 1+doxorubicin 25 mg/m^2 day 1+etoposide 100 mg/m^2 days 1–3+dacarbazine 375 mg/m^2 day 1+prednisolone 80 mg/m^{2}days 1–7+vincristine 1.6 mg day 8+bleomycin 10 mg/m^2 day 8+filgrastim 300 μg.

Patients underwent echocardiography and N-terminal pro-brain natriuretic peptide (NT-proBNP) measurement at the N. N. Blokhin Russian National Oncology Research Center. Clinical condition was evaluated, and perfusion SPECT was performed using 99mTc-MIBI with CT attenuation correction and electrocardiogram (ECG) – gating at the Russian National Cardiology Research Center before the beginning of PCT (cutoff point 1), after four courses of PCT, and the division of patients into two groups based on the presence of signs of cardiovascular toxicity (cutoff point 2). Cardioprotective treatment was recommended to patients meeting cardiovascular toxicity criteria (C+ group): changing the PCT regimen. Specifically, anthracycline drugs were excluded, and the following drugs were ordered: enalapril at the initial dose of 1.25 mg and bisoprolol 2.5 mg with slow titration to the maximum tolerated dose. Patients with preserved LVEF (C0 group) continued with the previous regimen of PCT. After another four courses of PCT, comparative studies of groups C+ and C0 were carried out (cutoff point 3).

The radionuclide imaging protocol included standard (summed stress score [SSS], summed rest score [SRS], summed difference score [SDS]) and quantitative (severity index [σS] and heterogeneity index [σH]) perfusion parameters, and volumetric (end-diastolic volume [EDV], end-systolic volume [ESV], LVEF) and velocity (peak ejection rate [PER] which characterizes global contractility and systolic function; peak filling rate [PFR] which characterizes diastolic function in general; mean filling rate during the first third of diastole [MFR/3]; time to peak filling [TTPF] in millimeters per second which indirectly characterizes the myocardial elasticity and ability to rapidly relax) parameters of LV contractility [4, 5].

Statistical analysis of the data obtained was performed using the MedCalc 15.8 and Microsoft Excel 2016 software suites. The nature of data distribution was evaluated using the Kolmogorov-Smirnov test. The quantitative data with normal distribution are expressed as the mean and standard deviation (M±σ), ordinal data (score) as the median and interquartile range (Me [Q1; Q3]). The categorical data are presented as category percentages (%). Statistical analysis processing was performed using the Student's t-test for normally distributed quantitative data or the Mann–Whitney/Wilcoxon rank-sum test for non-normally distributed quantitative data. The Fisher exact test was used to compare binary data in two groups (2×2 table). The chi-square test was used to compare other nominal data types in two or more groups (2×2 or more tables). The method of logistic regression was used in multivariate analysis. The differences were considered statistically significant at $p<0.05$.

Results

After four courses of PCT (cutoff point 1), 8 of 61 patients had both echocardiographic and C-SPECT signs of cardiovascular toxicity. Another 5 patients met the criteria for cardiovascular toxicity with only C-SPECT of the myocardium. Thus, the group of patients with signs of cardiovascular toxicity (C+ group) included 13 (21.3%) individuals. In this group, 76.9% of patients underwent repeat PCT, and the respective percentage in the C0 group was significantly lower (37.5%; p=0.03). The mean cumulative dose of doxorubicin was 480 [360; 840] mg/m^2 in the C+ group and 252.5 [240; 513.8] mg/m^2 in the C0 group. The mean therapeutic doses of bisoprolol and enalapril were 2.5 [2.5; 5.0] and 5.0 [5.0; 7.5] mg/day, respectively, after dose titration in the C+

group, patients were more likely to have a family history of cardiovascular diseases (p<0.01). However, there were no statistically significant age differences between the study groups (the mean age was 39±15 years in the general group, 39±15 years in the C0 group, and 40±16 years in the C+ group; p=0.83). The C+ and C0 groups also did not differ significantly in other signs (sex, body mass index, presence of co-morbidities).

There were no significant differences in the NT-proBNP levels between cutoff points 2 and 3, and there were no significant changes (92.7 [65.6; 124.0] pg/mL at cutoff point 2 and 99.3 [76.8; 126.9] pg/mL (p=0.20) at cutoff point 3 in the C0 group; 171.4 [146.8; 613.2] and 162.4 [118.9; 560.2] pg/mL (p=0.52), respectively, in the C+ group). However, there was a trend to a more pronounced increase in the levels of this biomarker in the C0 group (pΔ-C=0.08). The absolute values of NT-proBNP were increased in 11 (22.9%) patients at cutoff point 2 and 12 (25.0%) patients at cutoff point 3 in the C0 group. All 13 (100%) subjects in the C+ group had increased levels of this biomarker after doxorubicin therapy. However, after the administration of cardioprotective treatment, the NT-proBNP level remained elevated in 9 (69.2%) patients.

Echocardiography showed that LVEF decreased from 61±2 to 60±1% (p=0.04) in the C0 group between cutoff points 2 and 3. There was no statistically significant decrease in LVEF in the C+ group (51±5 and 50±6%, respectively; p=0.65).

At cutoff point 3, the stress test was performed in 44 (91.7%) patients in the C0 group and in 12 (92.3%) patients in the C+ group, and the pharmacological test in 4 (8.2%) and 1 (7.7%) patients, respectively. Negative results were reported in 47 (97.9%) patients in the C0 group and 13 (100.0%) patients in the C+ group. The test did not reach diagnostic criteria in 1 (2.1%) patient in the C0 group. Power working capacity was 5.7±1.3 MET in the C0 group, and 5.3±1.3 MET in the C+ group at cutoff point 2, and 5.4±0.9 and 5.4±1.8 MET, respectively, at cutoff point 3. There were no statistically significant MET differences between cutoff points in both groups (p=0.19 and p=0.87, respectively). Changes in the parameter studied were not statistically significant (ΔC0–0.2±1.2; ΔC+ – 0.1±1.3; pΔ=0.44).

The analysis of myocardial C-SPECT parameters showed that the systolic function continued to decline in the C0 group (LVEF decreased from 65±8 to 60±7%; p<0.01; Figure 1). PER decreased from 3.30±0.68 to 2.79±0.49 mL/sec (p<0.01), EDV increased from 74±19 to 82±18 mL (p=0.04) and ESV increased from 27±12 to 32±12 mL (p=0.04). The diastolic function of the LV also deteriorated: PFR decreased from 3.01±0.81 to 2.45±0.69 mL/sec (p<0.01) and MFR/3 decreased from 1.69±0.44 to 1.44±0.42 mL/sec (p<0.01), and TTPF also increased 160.50±33.66 to 179.15±12 msec (p<0.01). Changes in the parameters studies were significant in this group (pΔ<0.01 for all). LVEF decreased in 29 (60.4%) patients of this group with ΔEF=7±7% (p<0.0001).

Simultaneously, there were no statistically significant differences and changes in the C+ group (Figure 1). Further reduction of LVEF during cardioprotective treatment was observed in 4 patients by a mean of 9±2% (p<0.01). LVEF increased in 9 patients by a mean of 4±2% (p<0.01).

Standard myocardial perfusion parameters did not differ statistically significantly between the two groups (Table 1). The quantitative indicators of myocardial perfusion heterogeneity increased statistically significant in the C0 group (σS from 31.48±4.78 to 33.40±4.31; p=0.04; σH from 8.02±0.93 to 8.45±1.05; p=0.04); however, the gain between the two cutoff points was statistically significant only for σS. There are no statistically significant differences between the changes in parameters in the C+ group. However, the quantitative parameters of myocardial perfusion severity improved during cardioprotective treatment in 7 patients (ΔσS= – 1.37±1.29; p<0.05), and myocardial perfusion heterogeneity in 4 patients (ΔσH= –1.20±0.70; p<0.05) in this group.

Figure 2 shows changes in quantitative parameters of myocardial perfusion heterogeneity in the C0 and C+ groups as measured at cutoff point 3.

Figure 1. Left ventricular ejection fraction changes in the C0 and C+ groups based on the measurements at 3 cutoff points

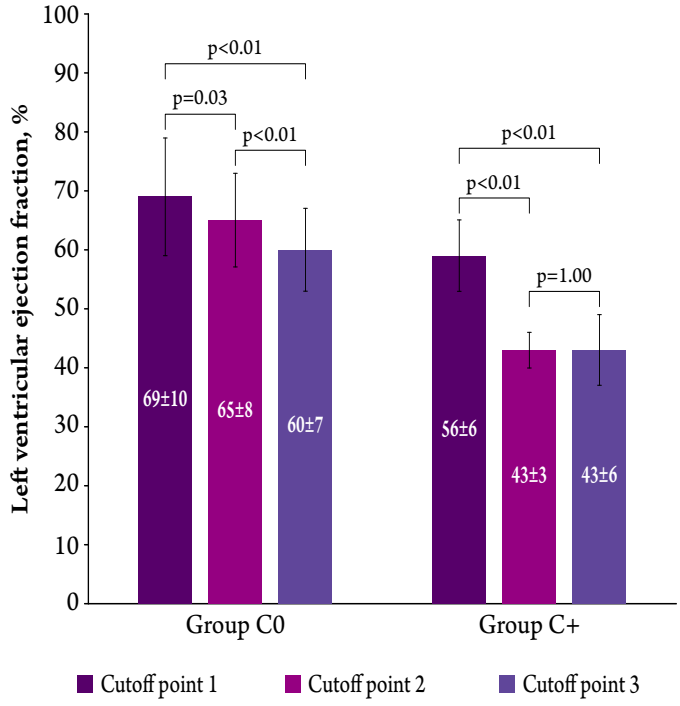

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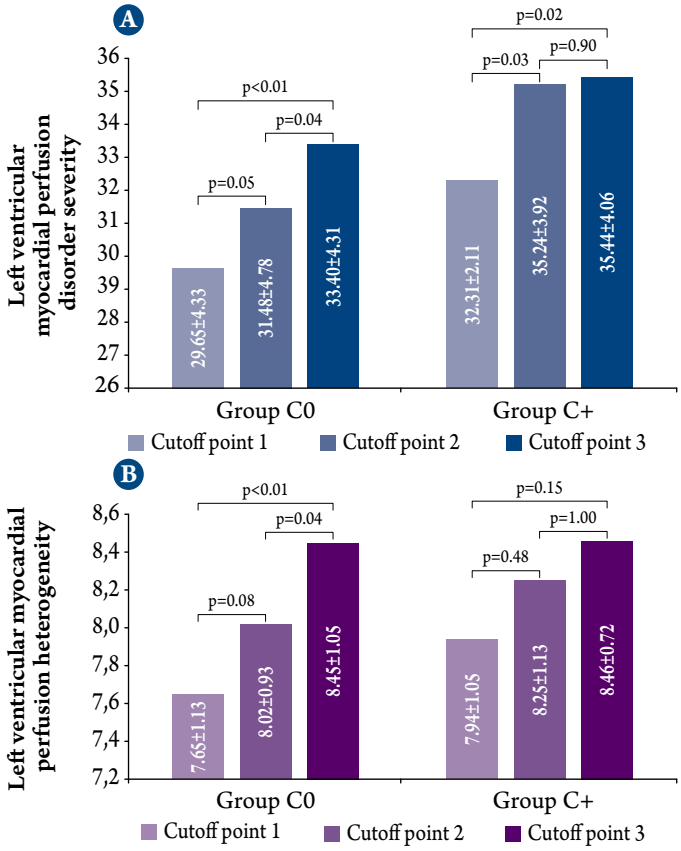
Table 1. Comparison of the parameters of left ventricular perfusion obtained by C-SPECT in the study groups between cutoff points 2 and 3

Parameters	C0 group (n=48)		p	C+ group (n=13)		p
	Cutoff point 2	Cutoff point 3		Cutoff point 2	Cutoff point 3	
SSS	6 [5; 8]	7 [5; 9]	0.36*	7 [6; 8]	5 [4; 7]	0.99*
SRS	3 [2; 5]	3 [1; 6]	0.43*	3 [2; 6]	3 [1; 4]	0.84*
SDS	3 [2; 4]	4 [3; 5]	0.63*	4 [3; 5]	3 [2; 4]	0.77*
σ_T	31.48±4.78	33.40±4.31	0.04**	35.24±3.92	35.44±4.06	0.90**
σ_H	8.02±0.93	8.45±1.05	0.04**	8.25±1.13	8.46±0.72	0.58**

*, Mann–Whitney U-test; **, t-test; SSS, summed stress score; SRS, summed rest score; SDS, summed difference score; σH, perfusion heterogeneity index; σS, perfusion severity index. C-SPECT, electrocardiogram-synchronized single-photon emission computed tomography.

Figure 2. Figure 2. Changes in left ventricular myocardial perfusion disorder severity σS (A) and heterogeneity σH (B) in the C0 и C+ groups based on the measurements at 3 cutoff points



Discussion

Cardiovascular toxicity of antitumor drugs, such as anthracycline antibiotics, is one of the key factors limiting their most effective use in oncology. The total cardiovascular toxicity rate was 21.3% in our study. Our findings are consistent with the literature. In the study by Cardinale et al. [6], which included 2,625 patients with a mean follow-up period of 5.2 years, cardiovascular toxicity developed in 9% of cases after the anthracycline therapy, with 98% of the cases occurring in the first year and being asymptomatic. In another study, including 630 patients with breast and lung cancers, anthracycline-related cardiovascular toxicity occurred in 5% of patients at the cumulative dose of 400 mg/m^2 and 48% at the cumulative dose of 700 mg/m^2. When asymptotic reduction of LVEF was included in the definition of cardiovascular toxicity, the incidence of cardiovascular complications was much higher and covered lower cumulative doses: 7%, 18%, and 65% at the cumulative doses of 150, 350, and 550 mg/m^2, respectively [6].

Cardiovascular toxicity induced by antitumor drugs is generally reversible, subject to early detection and timely treatment. Unfortunately, there are no reliable prevention and treatment strategies. Dexrazoxane is the only drug approved by the U.S. Food and Drug Administration and European Medicines Agency for preventing anthracycline-induced cardiovascular toxicity [7, 8]. The efficacy of dexrazoxane in maintaining myocardial functionality, reducing the incidence of subclinical cardiovascular toxicity, and clinically significant CVCs was confirmed by numerous studies [9, 10]. Meta-analysis of 10 studies of dexrazoxane (n=1,619) showed that the drug reduced the incidence of HF (odds ratio [OR] 0.29, 95% confidence interval [CI]: 0.20–0.41) [11]. However, the drug is not approved in the Russian Federation. Moreover, although dexrazoxane prevents anthracycline-induced cardiovascular toxicity, its cardioprotective effects are not sufficient because there are numerous cardiotoxic mechanisms of anthracyclines, and dexrazoxane inhibits only a few [12–15].

We evaluated the cardioprotective effects of a dual strategy involving changing the PCT regimen and ordering a combination therapy (enalapril at the initial dose of 1.25 mg and bisoprolol at the initial dose of 2.5 mg with slow titration to the maximum tolerated dose) in patients with anthracycline-induced cardiovascular toxicity. This approach was recommended initially to 8 patients with LVEF reduction in the echocardiography. However, another 5 patients had

reduced LVEF according to C-SPECT imaging. Given that echocardiography was performed at other health care facilities and by different operators, this may have caused an error in the evaluation of LVEF. It was agreed after careful discussion with oncologists to consider the C-SPECT data of these 5 patients and include them in the group of patients with signs of cardiovascular toxicity.

According to the laboratory analysis and the echocardiographic parameters evaluation, no statistically significant differences in the parameters of interest were found between the two cutoff points. Meanwhile, Tallaj et al. [16], who examined 25 patients with doxorubicin-induced cardiomyopathy and treated with ACE inhibitors (n=23) or angiotensin receptor blockers (n=2), and ACE inhibitors+beta-blockers (n=15), reported increased LVEF (26±9.2% vs. 35±16.5%; p=0.022) and decreased New York Heart Association functional class within the follow-up period of 71±58 months (p<0.003).

In the group of patients treated with ACE inhibitors+beta-blockers, a statistically significant improvement in LVEF was observed compared to the group treated with ACE inhibitors only (26%±10.0% vs. 37%±17.6%; p=0.028), with a strong trend toward LV function normalization (47% vs. 10%; p=0.054) [16].

The analysis of the C-SPECT data of the whole group showed no further decline of the LV contractile (systolic and diastolic) function during the cardioprotective treatment. However, there were also no signs of an LVEF increase. This may be due to insufficient time from the cardioprotective treatment to the cutoff point to assess the treatment efficacy. This result may also be due to the cardiovascular toxicity of other antitumor drugs or small sample size. Further study is required to answer this question.

A more thorough evaluation of this group found that LVEF continued to reduce by a mean of 9%±2% (p<0.01) in 4 (30.8%) patients. LVEF increased by a mean of 4%±2% (p<0.01) in 9 patients. During the cardioprotective treatment, the quantitative parameters of the LV myocardial perfusion severity in 7 patients (ΔσS= – 1.37±1.29; p<0.05), and the LV myocardial perfusion heterogeneity improved in 4 patients (ΔσH= – 1.20±0.70; p<0.05).

Conclusion

Our study demonstrates the efficacy of cardioprotective treatment in preventing further reduction of left ventricular ejection fraction and the development of heart failure in patients with signs of anthracycline-induced cardiovascular toxicity. Larger studies are needed, especially in risk groups, with a more extended follow-up period to determine whether these treatments remain effective in the long term and determine the best possible dosage and duration of cardioprotective therapy.

No conflict of interest is reported.

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