Rayimbek uulu N.[1], Pershukov I. V.[1, 2, 3], Shulzhenko L. V.[4, 5], Akbalaeva B. A.[1], Batyraliev T. A.[6], Gurovich O. V.[7], Kalmatov R. K.[1], Mamatova S. M.[1], Dzhainakbaev N. T.[2], Seidalin A. O.[2], Mansharipova A. T.[2], Kvasova M. V.[3], Vinogradskaya V. V.[8], Karben Z. A.[9], Fetzer D. V.[10], Ramazanov D. M. oglu[11], Kuznetsova T. N.[12], Ivanenkova E. Yu.[12], Rakhalskaya N. N.[2], Kamalieva M. R.[2]

[1] 1Osh State University, Osh, Republic of Kyrgyzstan
[2] Kazakhstan-Russian Medical University, Almaty, Republic of Kazakhstan
[3] Bobrov District Hospital, Bobrov, Voronezh Region, Russia
[4] Ochapovsky Research Institute Regional Clinical Hospital #1, Krasnodar, Russia
[5] Kuban State Medical University, Krasnodar, Russia
[6] Salymbekov University, Bishkek, Kyrgyz Republic
[7] Burdenko Voronezh State Medical University, Voronezh, Russia
[8] City of Health Clinic, Voronezh, Russia
[9] Sanko University, Şehitkâmil, Gaziantep, Turkey
[10] Municpal Clinical Hospital #52, Moscow, Russia
[11] Central Hospital of Oil Workers, Baku, Azerbaijan
[12] Voronezh Regional Clinical Hospital #1, Voronezh, Russia

The Joint Role of Serum Markers of Congestion or Myocardial Necrosis And Speckle Tracking Echocardiography in The Detection of Early Subtle Chemotherapy-Induced Cardiotoxicity in Women With Breast Cancer

Aim	To monitor the dynamics of biomarkers during chemotherapy, targeted chemotherapy and targeted monotherapy in patients with HER2-positive breast cancer (BC); to analyze the emergence timing of these changes; to compare early biochemical and echocardiographic criteria; and to determine the best time for assessing latent subclinical cardiac dysfunction.
Material and methods	Patients with BC (229 women aged 57±11 years) treated sequentially with anthracyclines, a combination of docetaxel and trastuzumab, and trastuzumab monotherapy were examined during three blocks of BC therapy until the development of clinical cardiotoxicity. Time-related changes in high-sensitivity cardiac troponin I, N-terminal pro-brain natriuretic peptide (NT-proBNP), left ventricular (LV) global longitudinal strain (GLS) and LV ejection fraction (EF) (up to 12 speckle-tracking echocardiograms/up to 12 laboratory tests) were analyzed. Clinical cardiotoxicity was defined as a symptomatic decrease in LV EF ≥10% from the baseline value of 54% or more.
Results	Clinically significant cardiotoxicity developed in 6.3-10.9% of cases depending on the treatment option for BC. Early manifestations of cardiotoxicity were detected already at 3 weeks after the start of the first course of chemotherapy. For the BC treatment with anthracyclines and targeted chemotherapy with docetaxel and trastuzumab, the markers of clinical cardiotoxicity were high-sensitivity cardiac troponin I, NT-proBNP and GLS LV. For the trastuzumab monotherapy, only GLS LV had a prognostic value. No statistically significant changes in the concentrations of high-sensitivity troponin I and NT-proBNP were found.
Conclusion	For timely detection of clinical cardiotoxicity, laboratory tests (high-sensitivity troponin I, NT-proBNP) and echocardiography (GLS LV) are recommended to be performed every 3 weeks before the next course of BC therapy. While doing so, their sensitivity will depend on the treatment option for BC.

Keywords	N-terminal pro-brain natriuretic peptide; high-sensitivity troponin I; left ventricular global longitudinal strain; speckle tracking echocardiography; cancer therapy-associated cardiac dysfunction; HER2-positive breast cancer; anthracyclines; docetaxel; trastuzumab
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Corresponding author Igor V. Pershukov. E-mail: cardio.ru@gmail.com

Introduction

Currently, cancer therapy is a rapidly developing area of knowledge. In economically developed countries; cancer morbidity is several times higher than in developing countries [1]. Furthermore, 52.7% of deaths in women and 58.9% of deaths in men are recorded in Asian countries due to the high density of the population (about 60% of the world's population) and low availability of medical care [1, 2].

For some patients with malignant neoplasms (MN), treatment becomes chronic, lasting for months and years and leading to the development of side effects and severe complications [3]. Cardiovascular complications limit the possibilities of MN therapy and cause interruption or even termination of treatment. Therefore, early detecting signs of cardiotoxicity becomes a priority task for both cardiologists and oncologists [4].

For cardiac injury, cardiomyopathy and chronic heart failure (CHF), the descriptive term "cancer therapy-related cardiac dysfunction" (CTCD) is recommended [5]. This term covers both a wide range of possible manifestations and the etiologic relationship with various cancer treatments, including chemotherapy, targeted drugs, immune therapy, and radiation therapy.

Aim

To track the dynamics of biomarkers during chemotherapy, chemo-targeted therapy, and monotargeted therapy in patients with HER2-positive breast cancer (BC), analyze the time of the appearance of these changes, compare early biochemical and echocardiographic criteria, and establish the best time to assess latent, subclinical CTCD.

Material and methods

All studies were conducted in consistency with the ethical standards set out in the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects" revised in 2013. All study protocols were approved by the ethical committees of the hospitals/institutions, and patients signed informed consent to participate before inclusion in the study.

Women aged 18 to 75 years were prospectively enrolled in 6 centers in 5 countries (Kyrgyzstan, Kazakhstan, Turkey, Azerbaijan, and Russia). Before inclusion in the study, oncologists established and verified the diagnosis of HER2-positive, locally advanced or metastatic BC. Treatment of BC was determined by oncologists in consistency with current guidelines on BC therapy [6].

The study design (Central Illustration) implied inclusion of patients who had not started BC treatment and did not have heart dysfunction. Inclusion criteria were normal levels of markers: creatine kinase MB fraction (CK-MB) <5.2 ng/ml, high-sensitivity (hs) troponin I <15.6 ng/l, N-terminal pro-brain natriuretic peptide (NT-proBNP) <125 pg/ml; left ventricular ejection fraction (LVEF) >54%; and baseline LV global longitudinal strain (LV GLS) in the normal range of -18% to -22%.

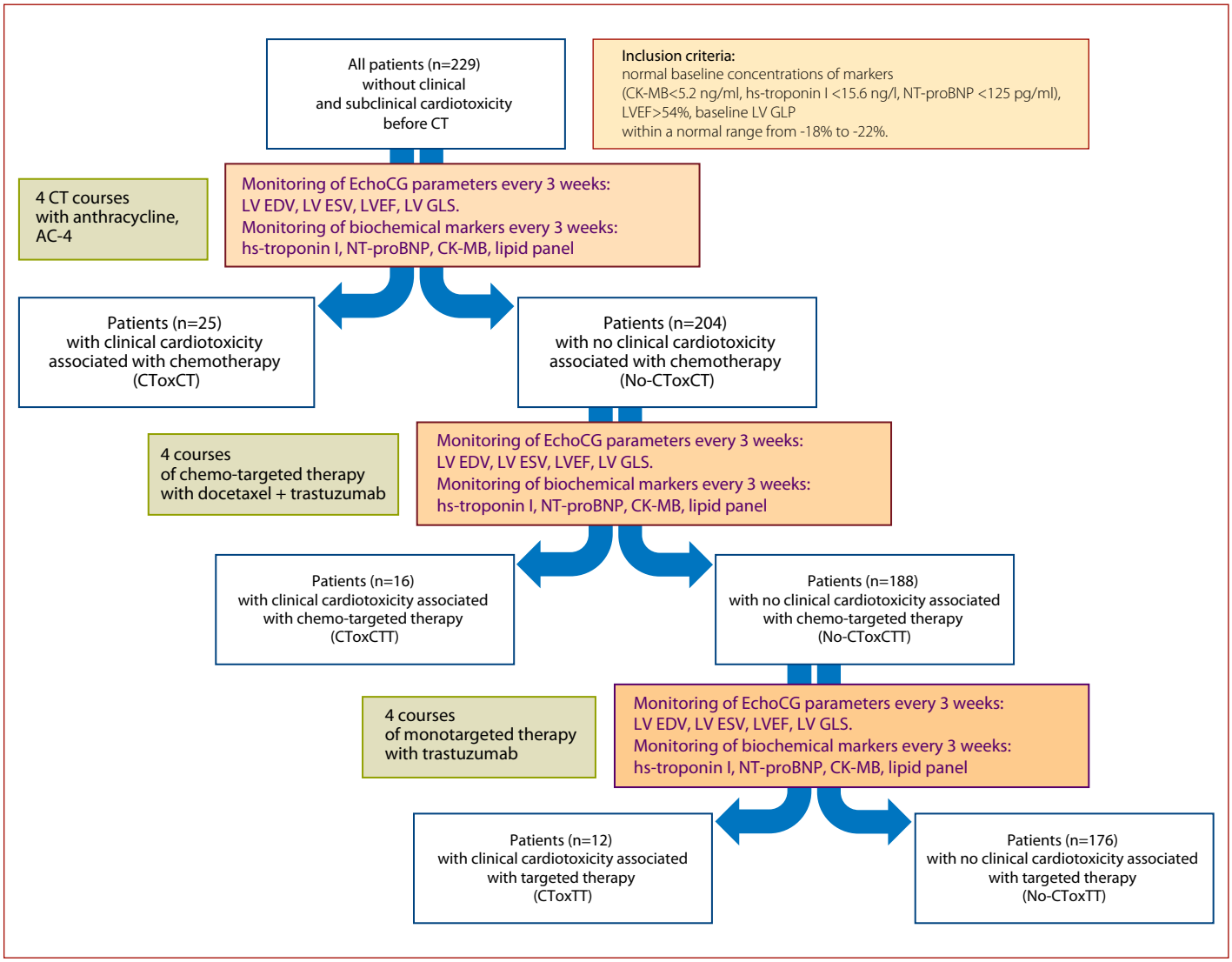
Exclusion criteria were ischemic heart disease, history of myocardial infarction, acute heart failure (HF) or CHF with LVEF <54%, elevated HF markers at baseline, myocardial overload or injury (CK-MB ≥5.2 ng/ml, hs-troponin I ≥15.6 ng/l, NT-proBNP ≥125 pg/ml), any forms of atrial fibrillation, other rhythm and conduction disorders requiring antiarrhythmic therapy, any previously known cardiomyopathy, severe valvular heart disease, hypertension with failure to achieve target blood pressure (BP), type 2 diabetes mellitus with glycated hemoglobin values >7.5%, stage IIIb or higher chronic kidney disease with an estimated glomerular filtration rate (GFR) <45/ml/min/m2.

Patients who did not complete the study protocol, discontinued chemotherapy early due to non-cardiac toxicity, or changed follow-up facilities were not included in this analysis.

Laboratory tests were performed in all patients before each course of BC therapy in each block (chemotherapy, chemo-targeted therapy, targeted therapy), including measurement of specific markers: hs-troponin I, NT-proBNP, CK-MB, and additionally, blood count, urinalysis, C-reactive protein (CRP), lipid panel (total cholesterol (TC), triglycerides, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C)), creatinine, urea, transaminases, lactate dehydrogenase, and other standard indicators. Also, all patients underwent speckle-tracking transthoracic echocardiography (EchoCG) with mandatory calculation of LV GLS before each course of therapy.

Serum hs-troponin I concentrations were measured with the Elecsys assay. The lower limit of detection was 3 ng/l (defined as undetectable levels), and values >15.6 ng/l (99th percentile of healthy individuals) were considered elevated. Serum concentrations of NT-proBNP were measured with the Elecsys assay, and val-

Central illustration. Study design



ues >125 pg/ml (99th percentile of healthy individuals) were considered elevated.

All echocardiographic studies were performed using a Philips Affiniti 70 ultrasonic system (Philips Health Care, USA) by a cardiologist skilled in imaging techniques with the automatic assessment of local myocardial contractility. Since there is a difference between vendors, we tried to avoid vendor-related differences in LV GLS assessment. Measurements were performed offline on an Xcelera workstation. Echocardiographic parameters included LV end-diastolic volume (EDV), LV end-systolic volume (ESV), and LVEF according to Simpson's cardiac chamber quantification guidelines. LV GLS was quantified using QLAB 10.5 and Automated Cardiac Motion Quantification (aCMQ) software.

All patients were recommended to undergo sequential adjuvant drug therapy for HER2-positive BC (Table 1).

According to this BC therapy protocol, we formed three comparison blocks: chemotherapy (CT), chemo-targeted therapy (CTT), and targeted therapy (TT). For each patient, 12 biochemical and 12 echocardiographic follow-up studies were scheduled before each BC therapy course. Patients who developed clinical CTCD by the end of each BC therapy block did not participate in next study blocks (Central Illustration).

Statistical analysis was performed with Statistica 12.5 software (Tulsa, USA). Quantitative variables are presented as mean ± standard deviation (SD), and categorical variables as absolute and relative frequencies n (%). Differences between patients with and without clinical cardiotoxicity were determined with Student's t-test for quantitative variables and chi-square test for categorical variables. When multiple tests were used, p-values were adjusted by the Benjamin-Hochberg method. Repeated measures analysis was used for differences between the CT, CTT, and TT blocks adjusted for multiple comparisons. Categorical variables in the repeated measures analysis were compared with the chi-square test, Z-test, and Fisher's exact test. Two-sided p-values <0.05 were considered statistically significant.

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Table 1. Treatment regimen of patients with HER2 positive locally advanced or metastatic breast cancer

Block	Cycles	Drugs	Treatment regimen for HER2+ BC
1, CT	1-4	ACx4 doxorubicin + cyclophosphamide	Doxorubicin 60 mg/m², IV, on day 1 + cyclophosphamide 600 mg/m², IV, on day 1
2, CTT	5-8	Docetaxel + trastuzumab	Docetaxel 75 mg/m², IV, on day 1, once in 3 weeks + trastuzumab 6 mg/kg (loading dose 8 mg/kg), IV, on day 1, once in 3 weeks
3, TT	9-12 and continuing	Trastuzumab	Trastuzumab 6 mg/kg, IV, once in 3 weeks until total duration of 12 months

BC, breast cancer; CT, chemotherapy; CTT, chemo-targeted therapy; TT, targeted (monotargeted) therapy; HER2+, HER2 positive molecular subtype of breast cancer.

Results

From January 2020 to January 2024, 229 patients were included in the study. Their baseline data are presented in Table 2.

Baseline speckle-tracking EchoCG showed normal results according to the inclusion criteria for the study (Table 3).

By the end of the CT block, clinically significant cardiac dysfunction (clinical CTCD) with a decrease in LVEF by >10% was diagnosed in 25 (10.92%) of 229 patients.

Table 2. Baseline data of patients before the start of BC therapy (n=229)

Parameter	Value
Mean age (range), years	57±11 (28-74)
Body mass index, kg/m²	31.9±4.9
SBP, mm Hg	134±10
DBP, mm Hg	79±8
Hemoglobin, g/l	126±13
Hematocrit, %	43±4
Erythrocytes, $\times 10^{12}$/l	4.9±0.8
Leukocytes, $\times 10^{9}$/l	5.6±1.7
ESR, mm/h	16±5
CRP, mg/l	6.2±1.1
TC, mmol/l	5.7±1.6
Triglycerides, mmol/l	1.7±0.6
HDL-C, mmol/l	1.1±0.3
LDL-C, mmol/l	4.0±1.3
Glucose, mmol/l	5.2±1.3
Potassium, mmol/l	4.6±0.6
Creatinine, μmol/l	77±17
Urea, mmol/l	6.6±2.9
CK-MB, ng/ml	2.7±1.7
High-sensitivity troponin I, ng/l	6.4±4.9
NT-proBNP, pg/ml	68±35

Data are presented as means and standard deviations (mean ±SD). BC, breast cancer; SBP, systolic blood pressure; DBP, diastolic blood pressure; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; CK-MB, creatine kinase MB fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide.

Based on the criterion of clinical CTCD after CT, two subgroups were formed: CToxCT (in which clinical CTCD developed after CT; n=25) and No-CToxCT (in which clinical CTCD did not develop after CT; n=204). Comparison of these subgroups revealed statistically significant differences in age: in the CToxCT subgroup, patients were significantly older: 65±12 years vs. 56±8 years (p<0.01). The CToxCT subgroup had a significantly higher body mass index: 34.5±5.5 kg/m² vs. 28.6±4.1 kg/m² (p<0.01) and higher systolic and diastolic BP at baseline: 139±12 mm Hg vs. 131±9 mm Hg (p<0.05) and 84±9 mm Hg vs. 77±8 mm Hg (p<0.05), respectively.

The lipid panel (Table 4) at the end of the CT block differed between the CToxCT and No-CToxCT subgroups: patients in the CToxCT subgroup had significantly higher concentrations of TC and LDL-C, although no significant differences were found at baseline.

Markers of HF and myocardial necrosis significantly changed starting already from the first CT course and throughout all 4 CT courses. It is important that the pronounced dynamics of these parameters were noted only in the CToxCT subgroup, while fluctuations in the No-CToxCT subgroup remained minor (Fig. 1; Table 5).

Cardioprotective therapy was administered to 25 patients in the CToxCT subgroup with clinical CTCD. Af-

Table 3. Baseline echocardiography data (n=229)

Parameter	Value
HR, beats/min	80±16
LV EDV, ml	90.5±20.5
LV ESV, ml	37.9±11.9
LVEF, %	60±4
LV GLS, %	–20.4±1.5
4-chamber view	–20.5±1.6
3-chamber view	–19.9±1.7
2-chamber view	–20.7±1.4

Data are presented as means and standard deviations (mean±SD). HR, heart rate; LV EDV, left ventricular end-diastolic volume; LV ESV, left ventricular end-systolic volume; LVEF, left ventricular ejection fraction; LV GLS, left ventricular global longitudinal strain.

Table 4. Lipid profile in subgroups at the end of CT block

Parameter	CToxCT (n=25)	No-CToxCT (n=204)	P
TC, mmol/l	6.4±1.8	5.1±1.5	<0.01
Triglycerides, mmol/l	1.9±0.6	1.6±0.6	>0.05
HDL-C, mmol/l	1.2±0.4	1.1±0.3	>0.05
LDL-C, mmol/l	4.2±1.2	3.7±1.1	<0.05

Data are presented as means and standard deviations (mean±SD). CT, chemotherapy; CToxCT, subgroup with clinical cardiotoxicity/CTCD following CT; No-CToxCT, subgroup without clinical cardiotoxicity/CTCD following CT; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

ter recovery of the heart function, their therapy for BC was returned, but they did not participate in the present study any more. We understood that after the anthracycline treatment, delayed CTCD may develop later and be superimposed on further treatment for BC in successive blocks. Nevertheless, we followed the schedule of the cancer treatment and monitored the same parameters in the same way before the start of each CTT course in the second CTT block (docetaxel + trastuzumab). It should be noted that at the start of CTT, LVEF was significantly lower than at the start of CT (59% before CT vs. 54% before CTT; p<0.05).

By the end of the CTT block, 16 (7.84%) of 204 patients had clinically significant CTCD with a decrease in LVEF by more than 10%.

As previously in the first block of BC therapy, significant differences in age were found between the CToxCTT (with clinical cardiotoxicity after CTT; n=16) and No-CToxCTT (with no clinical cardiotoxicity after CTT; n=188) subgroups. In the CToxCTT subgroup, patients were significantly older than in the subgroup without cardiotoxicity induced by docetaxel and trastuzumab by the end of the 8th CTT course (66±11 years vs. 54±8 years; p<0.01). Patients in the CToxCTT subgroup had a significantly higher body mass index (33.2±5.1 kg/m^2 vs. 29.2±3.3 kg/m^2; p<0.05).

As in the CT block, the CToxCTT subgroup had higher systolic BP before the start of CT (142±11 mm Hg vs. 127±8 mm Hg, p<0.01) and a tendency toward an increase in diastolic BP (82±9 mm Hg vs. 79±9 mm Hg, p>0.05).

Interestingly, the lipid panel was also different between the CToxCTT and No-CToxCTT subgroups at the end of the CTT block although no difference was detected at baseline, before the start of CTT (Table 6).

Figure 1. Dynamics of CK-MB (**A**), hs-troponin I (**B**) and NT-proBNP (**C**) concentrations in 3 CTox subgroups

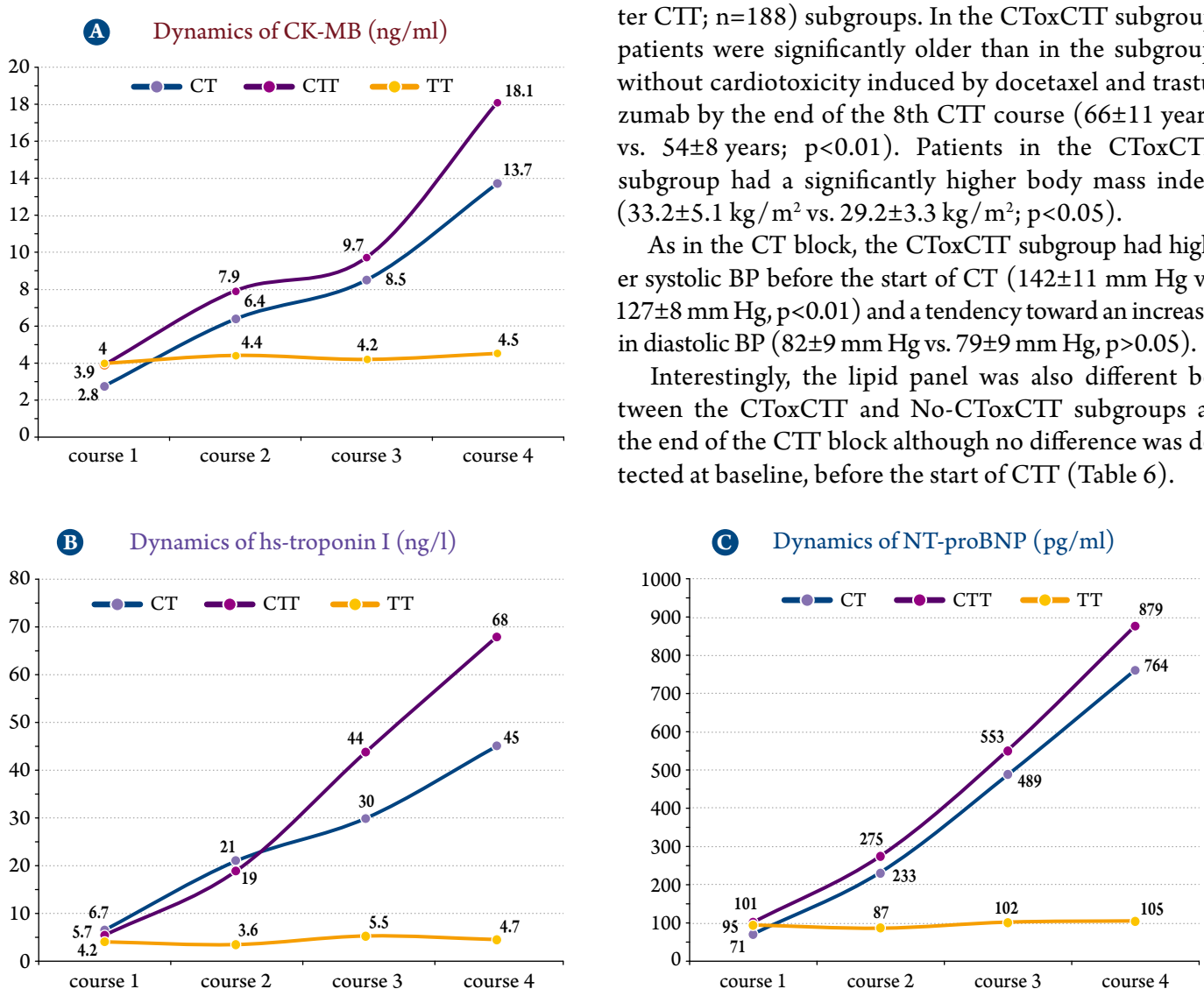

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Table 5. Dynamics of lab tests results in CTox subgroups (3 CTox subgroups and 3 No-CTox subgroups) during three blocks of BC therapy

Parameter		CT1	CT2	CT3	CT4	CTT1	CTT2	CTT3	CTT4	TT1	TT2	TT3	TT4
CK-MB, ng/ml	CTox	2.8±1.4	6.4±3.9	8.5±4.4	13.7±5.6	3.9±1.8	7.9±2.9	9.7±6.4	18.1±11.3	4.0±1.6	4.4±2.7	4.2±3.2	4.5±3.6
	No-CTox	2.7±1.6	3.3±1.9	3.9±2.2	4.6±2.4	3.3±1.2	3.9±1.7	4.5±2.4	5.1±2.9	4.1±2.7	4.7±3.9	4.4±3.7	3.8±3.1
hs-troponin I, ng/l	CTox	6.7±2.9	21±11.2	30±14.2	45±16.7	5.7±2.8	19±6.6	44±23	68±35	4.2±2.2	3.6±2.5	5.5±3.6	4.7±3.2
	No-CTox	6.3±2.6	8.8±3.7	10.2±3.5	13.1±4.8	5.5±3.0	7.9±5.1	9.9±6.5	12.7±8.6	4.6±2.5	4.9±3.1	3.9±2.6	2.3±2.1
NT-proBNP, pg/ml	CTox	71±19	233±74	489±132	764±285	101±43	275±89	553±137	879±355	95±57	87±59	102±67	105±72
	No-CTox	66±17	81±19	99±23	114±29	89±38	112±72	122±77	136±89	93±68	100±74	94±46	91±52

Data are presented as means and standard deviations (mean±SD). BC, breast cancer; CTox, any subgroup with clinical cardiotoxicity; No-CTox, any subgroup without clinical cardiotoxicity; CT, chemotherapy; CTT, chemo-targeted therapy; TT, targeted therapy; CK-MB, creatine kinase MB fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide.
Colors show significant dynamics in CT and CTT blocks.

As in the CT block, serological markers changed during all 4 courses of CT with pronounced dynamics only in the CToxCTT subgroup, while fluctuations in the No-CToxCTT subgroup remained statistically not significant (see Fig. 2 and Table 5).

All patients in the CToxCTT subgroup with clinical CTCD (n=16) received cardioprotective therapy and continued BC therapy after cardiac function recovery but did not participate further in the present study. Only 188 patients were included in the third TT block. The probability of toxicity superimposition after the anthracycline treatment existed, and it could have been noted in the CTT block and carried over to the TT block, but we could not isolate it and thus, took into account only the CTCD presence or absence.

By the end of the TT block, clinically significant CTCD with a LVEF decrease by more than 10% was observed in 12 (6.38%) of 188 patients.

As previously in the CT and CTT blocks, a statistically significant difference in age was found between the CToxTT (with clinical cardiotoxicity after TT; n=12) and No-CToxTT (with no clinical cardiotoxicity after TT; n=176) subgroups. Patients in the CToxTT subgroup were significantly older than those without cardiotoxicity associated with the trastuzumab treatment by the end of the 12th course of TT (63±10 years vs. 57±8 years; p<0.05). However, as distinct from the previous two blocks (CT and CTT), body weight indexes did not differ significantly (32.1±6.1 kg/m^2 vs. 30.5±5.3 kg/m^2, p>0.05). Patients in the CToxTT subgroup did not have a significantly higher body mass index; this trend was not significant in the TT block (32.1±6.1 kg/m2 vs. 30.5±5.3 kg/m2, p>0.05).

The pattern of changes in systolic and diastolic BP in the third block was consistent with that in the first two blocks. Patients in the CToxTT subgroup, who later developed CTCD, had higher values of systolic BP before the start of TT (134±12 mm Hg vs. 124±7 mm Hg, p<0.05); diastolic BP in patients with subsequent clinical CTCD was statistically significantly higher before the start of TT (86±10 mm Hg vs. 75±8 mm Hg, p<0.05).

The blood lipid profile did not show any differences between the CToxTT and No-CToxTT subgroups by the end of the TT block, just as it had no differences before the start of TT (Table 7).

In contrast to the dynamics in the previous CT and CTT blocks, in the TT block, specific markers did not change significantly during all 4 courses of trastuzumab therapy, regardless of whether clinical CTCD (CToxTT) developed by the end of the block or not (No-CToxTT). Some fluctuations of the markers in the CToxTT and No-CToxTT subgroups remained slight (Table 5 and Fig. 1).

Table 6. Lipid panel in subgroups at the end of CTT block

Parameter	CToxCTT (n=16)	No-CToxCTT (n=188)	p
TC, mmol/l	6.2±1.7	5.0±1.4	<0.01
Triglycerides, mmol/l	1.7±0.5	1.5±0.5	>0.05
HDL-C, mmol/l	1.2±0.3	1.1±0.3	>0.05
LDL-C, mmol/l	3.9±1.1	3.4±1.0	<0.05

Data are presented as means and standard deviations (mean±SD). CTT, chemo-targeted therapy; CToxCTT, subgroup with clinical cardiotoxicity following CTT; No-CToxCTT, subgroup without clinical cardiotoxicity following CTT; TC, total cholesterol; HDL, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Table 7. Lipid panel in subgroups at the end of TT block

Parameter	CToxTT (n=12)	No-CToxTT (n=176)	p
TC, mmol/l	5.3±1.6	5.2±1.4	>0.05
Triglycerides, mmol/l	1.6±0.4	1.5±0.4	>0.05
HDL-C, mmol/l	1.2±0.3	1.2±0.3	>0.05
LDL-C, mmol/l	3.8±1.0	3.7±1.1	>0.05

Data are presented as means and standard deviations (mean±SD). TT, targeted therapy; CToxTT, subgroup with clinical cardiotoxicity following TT; No-CToxTT, subgroup without clinical cardiotoxicity following TT; TC, total cholesterol; HDL, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

In all blocks, the development of clinical CTCD became the criterion for dividing patients into subgroups in each block of BC therapy in this study, and was considered when LVEF decreased by 10% or more from the initial value before the start of the treatment.

This study design allowed us to assess the incidence of clinical CTCD by showing its differences depending on the type of BC therapy, from 6.4% in the TT block to 10.9% in the anthracycline CT block; in the CTT block, the CTCD incidence was intermediate, 7.8%.

Negative dynamics of LV GLS occurred already after the first course of BC therapy in each treatment block (Fig. 2, A). According to data of speckle-tracking EchoCG, these negative dynamics led to a subsequent decrease in LVEF (thereby forming CTox subgroups) and the development of clinical CTCD (Fig. 2, B) by the end of each BC therapy block in all cases.

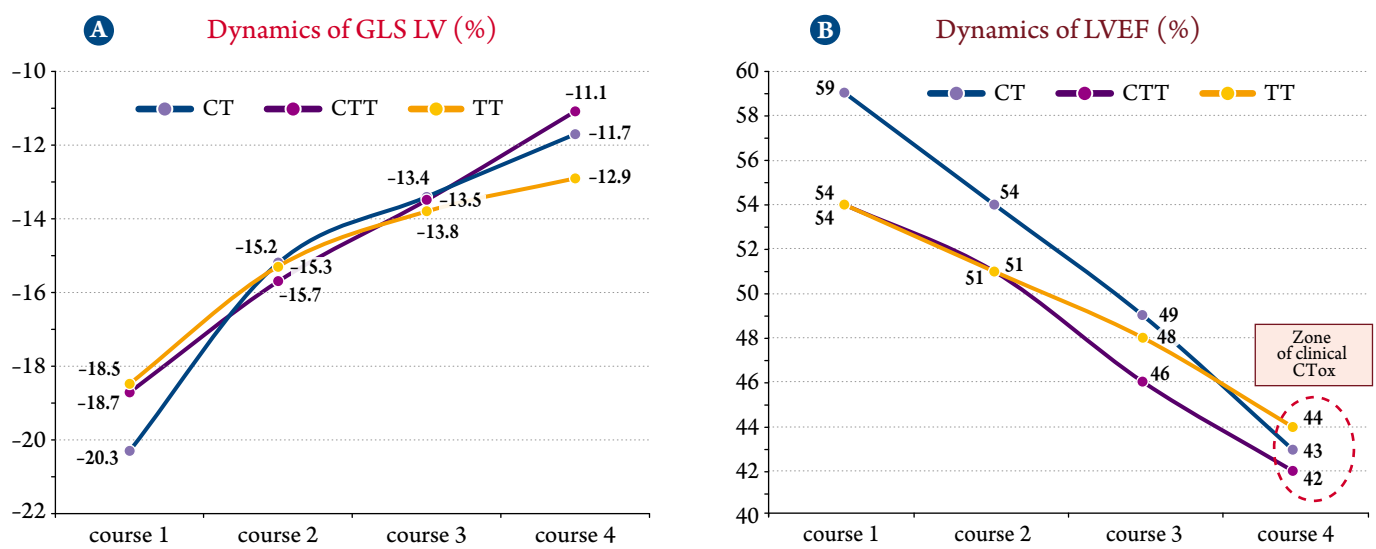
Discussion

Studying three blocks of BC therapy, where patients who developed clinical CTCD were excluded from further observation, showed that specific markers, such as hs-troponin I, NT-proBNP, CK-MB, and LV GLS derived from speckle tracking EchoCG, changed differently.

The early onset of subclinical CTCD was marked by statistically significant negative dynamics of hs-troponin I, NT-proBNP, CK-MB, as well as negative dynamics of 15% or more of LV GLS based on speckle-tracking EchoCG. Such synchronous negative dynamics of myocardial necrosis lab markers and LV GLS early after the first course of CT and CTT (3 weeks after the start of BC therapy before the next course) led to the development of clinical CTCD in 7.8% of cases during CTT and in 10.9% of cases during CT. However, this negative dynamics of markers for myocardial necrosis and hemodynamic overload did not manifest clinically significantly after courses of monotargeted trastuzumab therapy, when LV GLS remained the only early indicator of subsequent clinical CTCD at the end of the TT block, with the incidence of clinical toxicity of 6.4%.

Our previous study, which examined only the extended dynamics of echocardiographic parameters with the same block therapy for BC [7], showed that 5 to 16 weeks passed from the onset of the negative changes in LV GLS to the development of clinically significant CTCD with different block schemes of BC therapy. Moreover, we derived an "echo loop of cardiotoxicity" [8], which showed that all cases of clini-

Figure 2. Dynamics of LV GLS (A) and LVEF (B) in 3 CTox subgroups



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cally significant CTCD were preceded by subclinical CTCD with negative dynamics of LV GLS after the first course of BC therapy (i.e., after the first 3 weeks of BC treatment) in each block. This study confirmed that the negative dynamics of LV GLS is a reliable and the only instrumental prognostic factor for clinical CTCD. Laboratory markers of myocardial necrosis and hemodynamic overload are valid as prognostic indicators of subsequent clinical CTCD only for the anthracycline therapy or the docetaxel+trastuzumab therapy. In monotargeted trastuzumab therapy, it is not possible to rely on the negative dynamics of laboratory parameters. This study confirmed that the negative dynamics of LV GLS is a reliable and the only instrumental factor serving as a prognostic factor for clinical CTCD. Laboratory markers of myocardial necrosis and hemodynamic overload are valid as prognostic indicators of subsequent clinical CTCD only when analyzing anthracycline therapy or docetaxel therapy together with trastuzumab. In monotargeted trastuzumab therapy, it is not possible to rely on the negative dynamics of laboratory parameters.

The study by L. Sulaiman et al. [9] showed that during the treatment of BC in 74 women in Egypt who initially had neither risk factors for the development of cardiovascular complications, such as age over 65 years, arterial hypertension, type 2 diabetes mellitus, dyslipidemia, smoking, obesity with a body mass index above 30 kg/m2, nor cardiac dysfunction, i.e., their LVEF was >50%, the concentration of NT-proBNP during BC treatment increased from 34.4 to 73.5 pg/ml. However, the scatter of the NT-proBNP concentrations was 446 pg/ml at baseline and subsequently 956 pg/ml, which does not allow a correct analysis of the results. Negative dynamics of LV GLS were detected in 20% of women. Nevertheless, the authors, using ROC analysis, were able to reveal that an increase in NT-proBNP concentration by more than 2.2 times was 100% sensitive and 81% selective to clinically significant negative dynamics of LV GLS. However, this did not significantly affect LVEF, which was 61.8% at baseline and decreased during a single follow-up visit after 3 cycles of chemotherapy to 59.9% (p=0.031); Δ3D LVEF (%) was -2.0±7.4%. These authors considered cardiotoxicity as a symptomatic decrease in LVEF by >5% or an asymptomatic decrease in LVEF by >10%.

In a study performed in Kazakhstan, Zh. Tlegenova et al. [10] assessed cardiotoxicity in 120 patients with BC and found asymptomatic (subclinical) CTCD in 28.3% of cases. It is likely that such a high incidence of CTCD was due to the inclusion criterion of LVEF only >40% without symptoms of CHF. According to the BC treatment protocol, most women received CT with anthracyclines, and 2 small subgroups received combined CTT or trastuzumab monotherapy. The BC treatment was discontinued or modified when LVEF decreased to 41%. The authors noted statistically significant negative dynamics of LVEF and LV GLS as soon as after the second course of anthracycline CT. Among the biochemical parameters, only BNP showed negative dynamics, but its increase was noted in both subgroups, with and without cardiotoxicity. Thus, it is impossible to say anything about the sensitivity of laboratory parameters in identifying CTCD in this study. However, the authors were able to determine that a greater increase in the BNP concentration was associated with the development of CTCD.

In a single-center study of cardiotoxicity, Bhagat et al. [11] found that immediately after the end of anthracycline chemotherapy, subclinical CTCD was observed in 28% of cases, and 6 months later in the same patients, in 38% of cases. To identify subclinical CTCD, the authors needed to detect a decrease in LV GLS by 10% or more. This distinguishes this study from other studies where LV GLS was considered clinically significantly reduced with a drop of 15% or more. The milder criterion significantly overestimated the incidence of subclinical CTCD. In addition, the authors found that the difference in NT-proBNP concentrations was a predictor of subsequent CTCD, while the dynamics of the NT-proBNP concentration was a marker of subsequent CTCD.

The SUCCOUR study identified extended parameters in EchoCG that are important in the diagnosis of CTCD. In addition to the global longitudinal strain, these were the longitudinal strain in the 4-chamber view and the longitudinal strain in the 2-chamber view [12].

The study by B. Díaz-Antón et al. [13] was the most comparable with the present study. The authors established that during BC therapy, hs-troponin T gradually increased and reached a peak 96±13 days after the start of CT (p<0.001), and 62.5% of patients had elevated hs-troponin T values during the treatment. The NT-proBNP level increased after each anthracycline cycle (mean concentration before the cycle, 72±68 pg/ml and after the cycle, 260±187 pg/ml; p<0.0001). Clinical cardiotoxicity was observed in 9.7% of patients. Notably, the onset of clinical CTCD was detected on average after 5.2 months. In the group with cardiotoxicity, the decrease in LV GLS was more pronounced than in patients without cardiotoxicity (-17.6% vs. -21.4%; p=0.03) one month after the anthracycline treatment. As in our study, trastuzumab did not change serum concentrations of the biomarker. While baseline LVEF was an independent predictor of late cardiotoxicity (p=0.039), LV GLS

was an early predictor of cardiotoxicity (odds ratio: 1.12; 95% confidence interval: 1.02-1.24; p<0.05) after the anthracycline treatment. Neither hs-troponin T nor NT-proBNP concentrations can be considered as prognostic factors for cardiotoxicity after the trastuzumab therapy.

Thus, the present study determined the time of the earliest changes: 3 weeks from the start of BC therapy that leads to subsequent clinical CTCD. During therapy with anthracyclines or CTT with docetaxel and trastuzumab, hs-troponin I, NT-proBNP, and LV GLS equally early, as soon as after the first course of therapy, begin to change in those patients who will later manifest (develop) clinical CTCD. In the case of monotargeted therapy of BC with trastuzumab, LV GLS derived from daily monitoring of speckle tracking EchoCG remains the only early marker of subsequent clinical CTCD. LV GLS also changes early, already 3 weeks after the first course of TT. LV GLS is an important, and during trastuzumab monotherapy, the only early marker of subsequent clinical CTCD.

Recent analyses and meta-analyses of cardiotoxicity and cardioprotection [14] did not determine an earlier time of detecting early subclinical CTCD than the present study. Initial shifts in laboratory markers and echocardiographic parameters only complicate the analysis and do not provide additional practical benefits for primary prevention of clinical cardiotoxicity in BC therapy.

Conclusion

Left ventricular global longitudinal strain is the only early marker of subsequent clinical cardiotoxicity in any regimens of oncological pharmacotherapy for breast cancer, while the concentrations of high-sensitivity troponin I and pro-brain natriuretic peptide become markers of subsequent clinical cardiotoxicity only in the treatment of breast cancer with anthracyclines or with a combination of docetaxel and trastuzumab. All the earliest manifestations of subclinical cardiotoxicity, both laboratory and instrumental, emerge already after the first course of therapy for breast cancer, 3 weeks after the start of treatment.

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