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SHORT COMMUNICATION

Heart rate variability during and after chemotherapy with anthracycline in patients with breast cancer

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INTRODUCTION

Breast cancer is one of the most common types of cancer. Fortunately, the survival rate of breast cancer patients is quite high. However, cardiotoxicity after breast cancer treatment is a potentially life-threatening complication. Cardiac function can be assessed with echocardiography and biological markers [1]. However, there are few studies on heart rate variability (HRV) in patients with cancer, especially breast cancer, assessed with 24-h Holter electrocardiography (ECG). To our knowledge, no study has assessed HRV parameters immediately after chemotherapy infusion cessation. Low HRV has been shown to be a risk factor for cardiovascular diseases and a marker for all-cause mortality [2].

The present study aimed to assess early HRV changes during chemotherapy, assessed with 24-h Holter ECG in breast cancer patients.

METHODS

This prospective observational clinical study included 44 women without heart failure, who were diagnosed with breast cancer and were scheduled to undergo anthracycline-based chemotherapy. The patients were also administered 5-fluorouracil (20.0%), cyclophosphamide (96.7%), and docetaxel (13.3%). Informed consent was obtained from each patient, and the study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki.

Echocardiography was performed by an experienced echocardiographer using a Vivid E9 device (GE Medical Systems, Milwaukee, WI, USA) and a 4V-3D transducer (1.5––4.0 MHz). Transthoracic echocardiography was performed to evaluate left ventricular ejection fraction (LVEF) and diastolic parameters such as E/E' index, isovolumetric relaxation time, and E/A index. The Simpson method was used to assess LVEF in the two- and four-chamber views. Global longitudinal strain (GLS) was assessed by means of speckle tracking method. N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels were assessed using the electrochemiluminescence method.

Holter ECG (12-lead) was performed early after echocardiography examination in 44 patients at baseline. The measurements were performed over 24 h using a DMS300-4A measurement device (DM Software, Stateline, NV, USA). The following Holter ECG parameters were measured: mean heart rate, ventricular and supraventricular extrasystoles, and parameters of HRV, including standard deviation of all normal sinus RR intervals over 24 h (SDNN), standard deviation of the average normal sinus RR intervals for all 5-min segments (SDANN), mean of the standard deviations of all normal sinus RR intervals for all 5-min segments (SDNN index), root mean square of the successive normal sinus RR interval difference (rMSSD), and the percentage of successive normal sinus RR intervals > 50 ms (pNN50).

Holter ECG and echocardiography examination were performed at baseline, 24 h after the first cycle of drug administration, and 24 h after the last cycle of chemotherapy.

Changes during treatment were assessed and subsequently analysed using the Wilcoxon signed-rank test. The correlation analysis of measurable values was carried out with the Spearman Rank test. Statistical calculations were performed using the Statistica 12 software (StatSoft Inc., Tulsa, OK, USA). A p-value < 0.05 was considered statistically significant.

RESULTS

The study enrolled 44 women (mean age, 57.9 ± 6 years) with breast cancer treated with anthracycline. The mean

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Table 1. Changes in heart rate variability, echocardiography parameters, and NT-proBNP level in breast cancer patients during treatment

Characteristic	Before treatment	After the first cycle	p-value (changes after the first cycle of chemotherapy vs. baseline)	After chemotherapy cessation	p-value (alterations after chemotherapy cessation vs. baseline)
Medium HR [1/s]	76.4 ± 8	76.4 ± 9	0.78	78.4 ± 8	0.19
Time domain analysis:					
SDNN [ms]	130.5 ± 31	109.7 ± 31	< 0.01	109.7 ± 28	**0.03**
SDANN [ms]	120.7 ± 29	97.9 ± 26	**< 0.01**	102.8 ± 31	**0.01**
SDNN index [ms]	46.5 ± 14	44.1 ± 13	**0.01**	44.2 ± 15	0.31
rMSSD [ms]	27.1 ± 10	26.5 ± 8	0.23	27.5 ± 13	0.87
pNN50 [%]	7.3 ± 8	5.6 ± 5	0.10	6.8 ± 7	0.65
Frequency domain analysis:					
VLF [ms^2]	1340 ± 729	1263 ± 745	0.44	1165 ± 546	0.30
LF [ms^2]	434 ± 261	361 ± 228	0.14	375 ± 269	0.23
HF [ms^2]	153 ± 144	136 ± 70	0.57	124 ± 91	0.18
Echocardiography parameters:					
EF [%]	62.1 ± 5	65.3 ± 5	**0.004**	61.4 ± 5	0.29
E/E' ratio	9.2 ± 2	9.7 ± 3	0.87	10.1 ± 2.8	0.06
IVRT [ms]	108 ± 20	94 ± 21	**0.007**	101 ± 17	0.08
E/A ratio	0.89 ± 0.3	± 0.25	**0.007**	1.00 ± 0.2	**0.004**
Laboratory test:					
NT-proBNP [pg/mL]	95.4 ± 64	244.1 ± 156	**< 0.001**	349.6 ± 217	**< 0.001**

Data are shown as mean ± standard deviation. EF — ejection fraction; HF — high frequency; HR — heart rate; IVRT — isovolumetric relaxation time; LF — low frequency; NT-proBNP — N-terminal pro-B-type natriuretic peptide; pNN50 — percentage of successive normal sinus RR intervals > 50 ms; rMSSD — root mean square of the successive normal sinus RR interval difference; SDANN — standard deviation of the average normal sinus RR intervals for all 5-min segments; SDNN — standard deviation of all normal sinus RR intervals over 24 h; SDNN index — mean of the standard deviations of all normal sinus RR intervals for all 5-min segments; VLF — very low frequency

dose of doxorubicin was 258 ± 50 mg/m^2. The mean body mass index was 27.4 ± 4 kg/m^2. The mean LVEF and GLS at baseline were 62.1% and 19.4%, respectively. Among comorbidities diabetes mellitus was present in 14.6%, hypertension in 61%, and coronary artery disease in 2.4% of cases. Patients received antihypertensive drugs: angiotensin converting enzyme inhibitor (29.3%); β-blockers (21.6%); diuretics (22.2%); calcium-channel blockers (19.4%); and sartans (13.9%).

There were few changes in HRV 24 h after the first dose of anthracycline. SDNN, SDNN index, and SDANN decreased, and these changes were also present at the end of chemotherapy. In comparison, heart rate did not change significantly. The other parameters of HRV, including pNN50 and rMSSD, were worse after drug infusion; however, the changes were not significant. Additionally, there were no significant changes in parameters of Holter ECG, including frequency of supraventricular and ventricular extrasystoles and the duration of QTc interval during treatment. There were no changes during cancer treatment in frequent domain analysis either. All HRV and echocardiographic parameters are presented in Table 1.

Slight and transient improvement in ejection fraction (from 62.1% ± 5% to 65.3% ± 5%, p = 0.004) was noticed 24 h after the first dose of doxorubicin, which was not observed at the end of chemotherapy (61.4% ± 5%, p = 0.29). Moreover, the concentration of NT-proBNP significantly increased during treatment: 95.4 ± 64 pg/mL; 244.1 ± 156 pg/mL (p < 0.001); 349.6 ± 217 pg/mL (p < 0.001) before, after the first cycle, and at the end of chemotherapy treatment, respectively. There was a significant correlation between an increase in NT-proBNP levels and deterioration of HRV parameters such as SDNN (r_s: 0.55, p < 0.01); SDANN (r_s: 0.50, p = 0.01); SDNN index (r_s: 0.51, p = 0.01); rMSSD (r_s: 0.43, p = 0.03); and pNN50 (r_s: 0.49, p = 0.01) between baseline and the end of the treatment.

DISCUSSION

Arrhythmias can occur after anthracycline administration. Early complications usually occur shortly after drug administration and are generally transient. Late effects may be visible many years after chemotherapy cessation [3]. Life-threatening arrhythmias are quite rare. A previous hypothesis about

electrophysiological changes during anti-cancer treatment suggested the release of vasoactive factors into the blood soon after doxorubicin infusion [4]. Sympathetic activation after doxorubicin infusion supports this hypothesis and confirms the arrhythmogenic side effects of anthracyclines. The slight improvement of LVEF 24 h after doxorubicin infusion can be explained by the hypothesis of sympathetic activation. Additionally, antiemetic drugs, such as ondansetron, administered after chemotherapy infusion, might stimulate arrhythmias [5]. High frequencies of supraventricular and ventricular extrasystoles have been reported in patients after breast cancer treatment, and these extrasystoles have been shown to represent up to 72.4% of all registered rhythm disorders [6]. In the present study, the number of observed supraventricular and ventricular extrasystoles was within the reference range, and the increase in frequency was not significant. The low increase in frequency might be associated with the low doses of anthracyclines and the low frequency of antiemetic administration in our study.

Heart rate variability reflects cardiac autonomic function. In our study, HRV parameters such as SDNN, SDNN index, and SDANN were significantly worse 24 h after drug administration than at baseline. The worsening of HRV parameters in our study persisted until the end of chemotherapy. Our findings are consistent with those of other researchers, who showed a decrease in HRV parameters [7], suggesting the possibility of worsening sympathetic activation after drug infusion. It should be noted that Holter ECG was performed immediately after drug infusion, and many side effects of anti-cancer drugs are more strongly expressed in this period than a few weeks after administration. Additionally, the side effects of chemotherapy could cause unwillingness to perform normal daily activities. Moreover, fatigue after chemotherapy is known to lower sympathetic activity, which could have a negative effect on HRV parameters [8]. On the other hand, exercise training might enhance HRV parameters and reduce long-term mortality [9].

In our study changes in HRV parameters correlated with the NT-proBNP level measured between baseline and the end of the treatment. It was also noticed in other studies, which indicated that patients with a higher level of NT-proBNP had relatively higher sympathetic tone. This confirms our hypothesis of sympathetic activation [10]. However, we observed only slight changes in HRV parameters, and such findings do not outweigh the benefits of anti-cancer treatment.

In conclusion, HRV parameters such as SDNN, SDANN, and SDNN index might be lower immediately after doxorubicin infusion than at baseline, and these changes might be also present at the end of chemotherapy. Changes in HRV parameters measured between baseline and the end of the treatment significantly correlate with an increase in NT-proBNP level.

Conflict of interest: *none declared*

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