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Pharmacogenetics in treatment of anthracycline-induced cardiotoxicity in women without prior cardiovascular diseases

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ABSTRACT

Aim. To evaluate the role of polymorphisms in adrenoceptor beta 1 (*ADRB1*) (Arg389Gly, rs1801253) and angiotensin-converting enzyme (ACE) (I/D, rs4343) genes in assessing the effectiveness of β-blocker (carvedilol) and ACE inhibitor (enalapril) therapy in women with anthracycline-induced cardiotoxicity (AIC) without prior cardiovascular diseases (CVD) during 12-month follow-up.

Materials and methods. A total of 82 women (average age 45.0 (42.0; 50.0) years) with AIC and without prior CVD were included in the study. Echocardiography was performed and serum levels of NT-proBNP were determined at baseline and at 12 months after the enrollment. Gene polymorphisms in *ADRB1* and *ACE* genes were evaluated by polymerase chain reaction at baseline.

Results. Carriers of the G/G genotype in the *ADRB1* gene and G/G genotype in the *ACE* (I/D, rs4343) gene showed a significant increase in left ventricular ejection fraction (LVEF), a decrease in the size of the left ventricle (LV) and left atrium (LA), and a fall in the NT-proBNP level. Carriers of other genotypes had further progression of AIC which was manifested through a decrease in LVEF and an increase in the size of LV and LA.

Conclusion. Evaluation of gene polymorphisms in *ADRB1* (Arg389Gly, rs1801253) and *ACE* (I/D, rs4343) genes may be recommended before treatment initiation for AIC in women without prior CVD to determine who will benefit from carvedilol and enalapril therapy, as well as to identify a priority group of patients for personalized intensification and optimization of treatment for decreasing development of adverse cardiovascular events.

Keywords: anthracycline-induced cardiotoxicity, heart failure, gene polymorphisms, β-blocker, angiotensin-converting enzyme inhibitor

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Conformity with the principles of ethics. All patients signed an informed consent to participate in the study. The study was approved by the local Ethics Committee at Cardiology Research Institute of Tomsk NRMC.

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Фармакогенетика в лечении антрациклин-индуцированной кардиотоксичности у женщин без сопутствующих сердечно-сосудистых заболеваний

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РЕЗЮМЕ

Цель. Определить роль полиморфизмов генов β1-адренорецептора (*ADRB1*) (Arg389Gly, rs1801253) и ангиотензинпревращающего фермента (АПФ) (I/D, rs4343) в оценке эффективности терапии β-блокатором (карведилолом) и ингибитором АПФ (эналаприлом) у женщин с антрациклин-индуцированной кардиотоксичностью (АИК) и без сопутствующих сердечно-сосудистых заболеваний (ССЗ) в течение 12-месячного периода наблюдения.

Материалы и методы. В исследование включены 82 женщины в возрасте 45,0 (42,0; 50,0) лет с АИК и без ССЗ в анамнезе. Эхокардиографию и определение уровня NT-proBNP в сыворотке крови выполняли исходно и через 12 мес после включения в исследование. Оценку полиморфизмов генов *ADRB1* и *ACE* проводили с помощью полимеразной цепной реакции исходно.

Результаты. У носителей генотипа G/G гена *ADRB1* и генотипа G/G гена *ACE* (I/D, rs4343) диагностировано значительное увеличение фракции выброса левого желудочка (ФВ ЛЖ), уменьшение размеров ЛЖ и левого предсердия (ЛП), а также снижение уровней NT-proBNP. У носителей других генотипов наблюдалось дальнейшее прогрессирование АИК, что проявлялось снижением ФВ ЛЖ и увеличением размеров ЛЖ и ЛП.

Заключение. Оценка полиморфизмов генов *ADRB1* (Arg389Gly, rs1801253) и *ACE* (I/D, rs4343) может быть рекомендована до начала лечения АИК у женщин без ССЗ в анамнезе, чтобы определить, какие больные будут иметь преимущества от терапии карведилолом и эналаприлом, а также выделить приоритетную группу больных для персонифицированной интенсификации и оптимизации лечения с целью уменьшения развития неблагоприятных сердечно-сосудистых событий.

Ключевые слова: антрациклин-индуцированная кардиотоксичность, сердечная недостаточность, полиморфизмы генов, β-адреноблокатор, ингибитор ангиотензинпревращающего фермента

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INTRODUCTION

Anthracyclines are an important component of many chemotherapy regimens, but their use is associated with an increased risk of developing cardiotoxicity and heart failure (HF) [1]. As a result of the growing number of cancer survivors, the incidence of anthracycline-induced cardiotoxicity (AIC) is also increasing. However, neither optimal primary preventive strategies nor AIC-specific therapies have been developed for these patients [2]. Subclinical myocardial cell injury induced by anthracyclines is followed by asymptomatic left-sided heart failure and symptomatic HF, which can lead to irreversible cardiomyopathy. Although early AIC that develops in the first 12 months is often reversible, the late one involves a number of injuries that result in irreversible changes [3].

Treatment for patients with AIC currently includes standard therapies for congestive heart failure (HF) with ACE inhibitors, beta-blockers, and loop diuretics [4]. Enalapril and carvedilol are some of the main drugs for AIC treatment that appear effective in reducing the rates of left ventricular systolic dysfunction and preventing left ventricular ejection fraction (LVEF) decline in patients with AIC [2, 5, 6]. However, not all patients respond to therapy with these drugs. There are responders that have an increase in LVEF after the onset of congestive HF and non-responders that have no increase or even a decrease in LVEF despite receiving optimal drug therapy [7]. Genetic factors may be crucial in a patient's response to treatment and may help identify a subset of HP patients with AIC who might benefit from personalized intensification and optimization of treatment in order to reduce the development of adverse cardiovascular events [8].

Therefore, the aim of the study was to evaluate the role of polymorphisms in beta1-adrenoceptor (*ADRB1*) (Arg389Gly, rs1801253) and angiotensin-converting enzyme (ACE) (I/D, rs4343) genes in assessing the effectiveness of β-blocker (carvedilol) and ACE inhibitor (enalapril) therapy in women with anthracycline-induced cardiotoxicity (AIC) and without concomitant cardiovascular diseases (CVD) during a 12-month follow-up period.

MATERIALS AND METHODS

The study was conducted in accordance with the Declaration of Helsinki and was approved by the local Ethics Committee at Cardiology Research Institute, Tomsk National Research Medical Center. All patients signed an informed consent to participate in the study.

The study was prospective, observational, and single-center. A total of 82 women with AIC which developed 12 months after chemotherapy were enrolled in the study from February 2019 to February 2020.

Inclusion criteria were the following: 1) women with breast cancer who did not have a history of cardiovascular diseases and who developed AIC; 2) cancer treatment they received was either a combination of doxorubicin and cyclophosphamide (AC regimen), or a combination of doxorubicin, cyclophosphamide, and docetaxel (TAC regimen); 3) NT-proBNP levels ≥ 125 pg / ml; 4) breast cancer remission.

Criteria for the development of AIC included reduction of LVEF by ≥ 10 points from the baseline value or LVEF value of less than 55% with symptoms of HF and NT-proBNP levels ≥ 125 pg / ml 12 months after chemotherapy.

Exclusion criteria were the following: 1) type 1 and 2 diabetes mellitus; 2) coronary heart disease; 3) hypertension; 4) valve defects and prior cardiomyopathies of any etiology; 5) HF with an alternative cause of manifestation (severe lung diseases, primary pulmonary hypertension, anemia, body mass index > 50 kg / m^2); 6) previous treatment with any cardiovascular drugs, including ACE inhibitors and β-blockers; 7) concomitant severe renal or hepatic failure, or multiple organ dysfunction syndrome; 8) indications of poor drug tolerance; 9) chronic alcoholism or mental disorders; 10) ovarian pathology or hormonal imbalance.

Blood samples were obtained by venipuncture and adequate serum samples after centrifugation were stored at −24 °C with one freeze – thaw cycle. The serum levels of NT-proBNP were determined using an enzyme-linked immunosorbent assay (Biomedica Immunoassays, Austria).

Buccal epithelium was taken to determine gene polymorphisms. DNA was isolated from buccal epithelial cells using phenol - chloroform extraction. Genotyping of the *ADRB1* gene (polymorphism Arg389Gly, rs1801253) and I/D of the *ACE* gene (I/D, rs4343) was carried out by the real-time polymerase chain reaction.

The Hardy – Weinberg equilibrium was used to monitor genotyping results, testing was conducted using an online program on the website of the Institute of Human Genetics (http://ihg2.helmholtz-muenchen.de/cgi-bin/hw/hwa1.pl).

All patients received β-blocker (carvedilol) and ACE inhibitor (enalapril) therapies as AIC treatment. Drugs were titrated to the maximum tolerated dose. Given the fact that study participants were women without a history of cardiovascular diseases, the average up-titrated dose of carvedilol was 50 (25; 50) mg / day and that of enalapril was 10 (10; 20) mg / day.

An unfavorable course of AIC was defined as new or aggravating symptoms / signs of HF, reduction of LVEF by more than 5% 12 months after treatment initiation, or an increase in New York Heart Association (NYHA) class by 1 or more functional classes. Patients who did not meet these criteria had a favorable course of AIC.

Statistical processing of the results was carried out using Statistica 10.0 R software package version 2. Data were presented as the median and the interquartile range *Me* (Q_{25}; Q_{75}). To test statistical hypotheses, the Mann – Whitney test was used to analyze quantitative variables when comparing two groups. In the analysis of qualitative characteristics, the contingency tables were analyzed using the Pearson's χ2 test. If there were cells with an expected frequency of less than 5, then the two-sided Fisher's exact test or the Yates's correction was applied (for 2 × 2 tables). Odds ratios (OR) for gene polymorphisms were determined using logistic regression models. All *p* values were two-tailed. The differences were considered statistically significant at *p* value of 0.05 or less. Power calculation for the gene polymorphism test was 72.6%.

RESULTS

Initially, we examined a total of 303 women aged 45.0 (42.0; 50.0) years with breast cancer and without cardiovascular diseases and cardiovascular risk factors (LVEF of 67.0 (62; 70) %), who received chemotherapy. The cumulative dose of doxorubicin was 300–360 mg / m^2. 12 months after chemotherapy, 82 patients developed symptoms of HF (NYHA FC I0III) and had reduction of LVEF by 25.2%: from 65.5 (61; 70) to 49 (47; 52) %. These patients were included in the study, and for the treatment of AIC, they were prescribed carvedilol and enalapril at the maximum tolerated doses.

All patients were examined after 12 months of treatment and were divided into two groups: group 1 (n = 31) included patients with an unfavorable course of AIC, group 2 (n = 51) consisted of patients with a favorable course of the disease. Baseline demographic and clinical characteristics did not differ between the groups (Table 1). Baseline echocardiography parameters were also the same in both groups. However, 12 months after treatment initiation, in group 1, LVEF significantly ($p < 0.001$) decreased by 10.0% from 50 (47; 53) to 45 (44; 49) %; end-systolic diameter (ESD) increased by 3.0% ($p = 0.037$), end-diastolic diameter (EDD) rose by 4.0% ($p = 0.001$), left atrial (LA) size increased by 3.2% ($p = 0.001$), and 6-minute walk test (6MWT) distance decreased ($p = 0.046$) by 5.4%. In group 2, LVEF significantly ($p = 0.005$) increased by 6% from 49 (46; 51) to 52 (47; 55) %; the levels of NT-proBNP decreased by 22.5% ($p < 0.001$), and 6MWT distance increased ($p = 0.011$) by 11.6% (Table 2).

The presence of the C/G genotype in *ADRB1* rs1801253 (odds ratio (OR) = 2.01; $p = 0.004$) and the A/A genotype in *ACE* rs4343 (OR = 4.21; $p = 0.003$) was associated with further reduction of LVEF and progression of HF symptoms despite the therapy. The G/G genotype in the *ADRB1* rs1801253 gene (OR = 0.55; $p < 0.001$) and the G/G genotype in the *ACE* rs4343 gene (OR = 0.65; $p = 0.001$) were significantly associated with the improvement in HF symptoms and an increase in LVEF by 6%. Thus, patients with these genotypes may benefit from β-blocker (carvedilol) and ACE inhibitor (enalapril) therapy for AIC (Table 3).

No differences in echocardiography parameters and NT-proBNP levels were found at baseline and after 12 months of follow-up depending on NYHA functional class. The dynamics of the echocardiography parameters, NT-proBNP levels, and 6MWT distance during the follow-up were analyzed depending on polymorphisms in *ADRB1* (Arg389Gly, rs1801253) and *ACE* (I/D, rs4343) genes (Table 4). Women with the G/G genotype in the *ADRB1* gene (Arg389Gly, rs1801253) had the absolute benefit from carvedilol and enalapril therapies. In these patients, LVEF significantly ($p < 0.001$) increased by 10.7% from 50 (48; 51) to 56 (53; 57) %, ESD and EDD decreased by 5.8 ($p < 0.001$) and 6.0% ($p < 0.001$), respectively; LA size decreased by 9.7% ($p < 0.001$), 6MWT distance increased ($p = 0.008$) by 4.7%, and NT-proBNP decreased by 34.8% ($p < 0.001$). In carriers of the C/C and C/G genotypes, HF progressed further, which was manifested through a decrease in LVEF and an increase in LV and LA dimensions.

Women with the G/G genotype in the *ACE* (I/D, rs4343) gene benefited from carvedilol and enalapril therapies as well. In these patients, LVEF significantly ($p = 0.002$) increased by 7% from 50.5 (47; 51) to 54 (50; 57) %, ESD and EDD decreased by 5.3 ($p = 0.007$) and 3.0% ($p = 0.038$), respectively; LA size decreased

by 3.3% (p = 0.012), and NT-proBNP decreased by 20.4% (p = 0.007). In carriers of the A/A genotype, HF progressed further, which was manifested through a decrease in LVEF and an increase in LV dimensions, however, NT-proBNP levels tended to decrease by 20% (p = 0.052). Echocardiography parameters in patients with the A/G genotype in the *ACE* (I/D, rs4343) gene did not change, but NT-proBNP levels significantly decreased by 19.6% ($p < 0.001$).

Table 1

Clinical and demographic characteristics of patients at the time of inclusion in the study

Parameters	Group 1, n = 31	Group 2, n = 51	p
Age, years, *Me* (Q_{25}; Q_{75})	50 (47; 52)	48 (45; 50)	0.066
Body mass index, kg / m^2, *Me* (Q_{25}; Q_{75})	23.7 (21.3; 26.2)	24.3 (21; 26.3)	0.601
Heart rate, bpm, *Me* (Q_{25}; Q_{75})	75 (68; 83)	75 (69; 81)	0.825
Systolic blood pressure, mm Hg, *Me* (Q_{25}; Q_{75})	115 (110; 120)	115 (110; 120)	0.744
Diastolic blood pressure, mm Hg, *Me* (Q_{25}; Q_{75})	70 (70; 80)	75 (70; 80)	0.012
NYHA Class Class I, n (%) Class II, n (%) Class III, n (%)	 16 (51.6) 13 (41.9) 2 (6.5)	 26 (50.9) 20 (39.1) 5 (9.8)	 0.987 0.675 0.423
Smoking, n (%)	5 (16.1)	8 (15.7)	0.143
COPD, n (%)	4 (12.9)	7 (13.7)	0.981
Childbearing potential, n (%)	10 (32.2)	18 (35.3)	0.877
Menopause, n (%)	21 (67.8)	33 (64.7)	0.191
GFR, ml / min / m^2, *Me* (Q_{25}; Q_{75})	89 (78; 96)	88 (76; 98)	0.876
Six-minute walk test distance, m, *Me* (Q_{25}; Q_{75})	426 (349; 482)	426 (359; 472)	0.601
Total cholesterol, mg / dl, *Me* (Q_{25}; Q_{75})	93.6 (83.7; 102.6)	94.5 (84.6; 102.6)	0.882
LDL, mg / dl, *Me* (Q_{25}; Q_{75})	43.2 (39.6; 50.4)	43.2 (39.6; 50.5)	0.475
HDL, mg / dl, *Me* (Q_{25}; Q_{75})	41.44 (36.0; 42.2)	39.6 (36.0; 43.2)	0.323
Glucose, mmol / l, *Me* (Q_{25}; Q_{75})	5.3 (4.2; 6.1)	5.4 (4.1; 6.0)	0.541
Hemoglobin, g / l, *Me* (Q_{25}; Q_{75})	109.5 (100; 117)	109.5 (99; 117,5)	0.798
NT-proBNP, pmol / ml, *Me* (Q_{25}; Q_{75})	353.9 (265.4; 412.5)	317 (253; 372.9)	0.163

Note: GFR – glomerular filtration rate (CKD-EPI); HDL – high density lipoproteins; LDL – low density lipoproteins.

Table 2

Dynamics of echocardiography parameters, NT-proBNP levels, and 6-minute walk test distance during the follow-up period *Me* (Q_{25}; Q_{75})

Parameters	Before chemotherapy		p	12 months after chemotherapy (before carvedilol and enalapril treatment initiation)		p	12 months after carvedilol and enalapril treatment initiation		p
	Group 1, n = 31	Group 2, n = 51		Group 1, n = 31	Group 2, n = 51		Group 1, n = 31	Group 2, n = 51	
LVEF, %	67 (63; 70)	65 (60; 69)	0.119	50 (47; 53)	49 (46; 51)	0.117	45 (44; 49)#	52 (47; 55)#	<0.001
LA, mm	28 (26; 31)	28 (25.5; 31)		31 (29; 33)	31 (28; 32)	0.064	32 (30; 34)#	29 (27; 30)#	<0.001
EDD, mm	41 (39; 44)	42 (40; 44)	0.396	48 (45; 51)	50 (46; 51)	0.252	50 (48; 52)#	48 (47; 50)	0.005
ESD, mm	30 (27; 32)	29 (27; 30)	0.336	37 (34; 39)	36 (32; 38)	0.191	38 (37; 39)#	35 (32; 37)	<0.001
NT-proBNP, pg/ml	52.7 (45.9; 60.8)	51.1 (45; 61.9)	0.775	353.9 (265.4; 412.5)	317 (253; 372.9)	0.163	314.5 (259.3; 357.8)	245.6 (211.9; 276.8)#	<0.001
6-MWT distance, m	576 (552; 592)	575 (560; 589)	0.924	426 (349; 482)	426 (359; 472)	0.149	403 (341; 436)#	482 (375; 476)#	0.008

Note: here and in Table 4: 6-MWT – 6-minute walk test; LVEF – left ventricular ejection fraction; LA – left atrium; EDD – end-diastolic diameter; ESD – end-systolic diameter; NT-proBNP – N-terminal pro-B-type natriuretic peptide; # – statistically significant differences in comparison with the baseline levels.

Table 3

The frequency of genotypes, n, %, and odds ratio

Gene	Genotype	Group 1, *n* = 31	Group 2, *n* = 51	OR	95% confidence interval (CI)	χ2	*p*
ADRB1 (Arg389Gly, rs1801253)	C/C	10 (32.3)	11 (21.6)	0.98	0.87–1.12	1.16	0.282
	C/G	21 (67.7)	18 (35.3)	2.01	1.91–2.27	8.13	**0.004**
	G/G	0 (0.0)	22 (43.1)	0.55	0.18–1.11	18.27	<0.001
ACE (I/D, rs4343)	A/A	16 (51.5)	10 (19.6)	4.21	2.89–11.54	9.12	**0.003**
	A/G	14 (45.3)	24 (47.1)	0.98	0.9–1.13	0.04	0.867
	G/G	1 (3.2)	17 (33.3)	0.65	0.38–1.43	10.20	**0.001**

Table 4

Dynamics of echocardiography parameters, NT-proBNP levels, and 6-minute walk test distance during the follow-up period depending on gene polymorphisms in *ADRB1* (Arg389Gly, rs1801253) and ACE (I/D, rs4343) genes, *Me* (Q_{25}; Q_{75})

Parameters	12 months after chemotherapy (before carvedilol and enalapril treatment initiation)			*p*	12 months after carvedilol and enalapril treatment initiation			*p*
	ADRB1 (Arg389Gly, rs1801253)				*ADRB1* (Arg389Gly, rs1801253)			
	C/C, n = 21	C/G, n = 39	*G/G, n* = 22		C/C, *n* = 21	C/G, *n* = 39	G/G, *n* = 22	
LVEF, %	49 (47; 51)	49 (46; 53)	50 (48; 51)	0.859	48 (45; 49)#	46 (44; 49)#	56 (53; 57)#	<0.001
LA, mm	30 (29; 33)	31 (28; 33)	31 (29; 32)	0.431	31 (30; 33)#	31 (29; 33)	28 (27; 30)#	<0.001
EDD, mm	49 (45; 50)	48 (46; 52)	50 (48; 51)	0.377	49 (48; 51)#	48 (46; 52)#	47 (46; 48)#	<0.001
ESD, mm	35 (33; 38)	37 (33; 39)	34 (32; 37)	0.335	37 (35; 38)#	37 (36; 39)#	32 (31; 34)#	<0.001
NT-proBNP, pg/ml	324.8 (285.7; 394.7)	318.9 (259.7; 381.8)	327.5 (260.1; 387.5)	0.976	311.7 (248.9; 350.9)	276.8 (242.8; 337.8)#	213.55 (195.3; 256.7)#	<0.001
6-MWT distance, m	426 (359; 445)	433 (348; 488)	423 (364; 467)	0.667	403 (350; 418)#	430 (345; 476)	444 (402; 476)#	0.038
ACE (I/D, rs4343)				*p*	*ACE* (I/D, rs4343)			*p*
A/A, n = 26		A/G, n = 38	G/G, n = 18		A/A, n = 26	A/G, n = 38	G/G, n = 18	
LVEF, %	52 (47; 53)	48.5 (46; 51)	50.5 (47; 51)	0.052	48 (45; 50)#	47 (45; 51)	54 (50; 57)#	0.002
LA, mm	29 (27; 32)	31 (29; 33)	30 (29; 32)	0.125	32 (29; 33)#	32 (29; 33)	29 (27; 30)#	0.031
EDD, mm	49.5 (45; 50)	48 (46; 50)	50 (49; 52)	0.192	50 (48; 52)#	48 (47; 50)	48.5 (47; 50)#	0.116
ESD, mm	35.5 (33; 37)	36 (33; 39)	38 (34; 40)	0.237	37 (35; 38)#	36 (33; 38)	36 (32; 37)#	0.341
NT-proBNP, pg/ml	359.5 (265.4; 421.5)	321.1 (259.7; 387.5)	314.1 (279.6; 372.9)	0.678	287.6 (245.6; 350.9)	258 (214.7; 314.5)#	249.9 (195.3; 267.8)#	0.035
6-MWT distance, m	397 (335; 450)	433.5 (358; 482)	426 (378; 473)	0.252	397 (335; 432)	413.5 (376; 474)	449 (421; 487)	0.015

DISCUSSION

AIC largely develops due to doxorubicin-induced free radical formation through mitochondrial redox cycling of doxorubicin in cardiomyocytes, which ultimately leads to LV dysfunction and in the most severe cases – to irreversible congestive HF [4]. The clinical implications of this cardiotoxicity become more important with the increasing use of cardiotoxic drugs [9] and the growing number of cancer survivors, which leads to an increase in the incidence of AIC [3]. However, the optimal strategy for preventing and managing AIC requires further research. Various groups of drugs for AIC treatment and prevention are currently being investigated. ACE inhibitors and β-blockers slow down the progression of LV dysfunction in HF, but their effectiveness in AIC treatment is still controversial.

Oxidative stress as the main mechanism for the development and progression of AIC may also contribute to contractile LV dysfunction, cardiac remodeling, lethal arrhythmias, and sudden cardiac death. Several medications are known to have antioxidant effects, including some ACE inhibitors and β-blockers. Carvedilol is a non-selective β-blocker with antioxidant properties [10]. The results obtained in several studies indicate that carvedilol has a protective effect for primary prevention of AIC [2] and may inhibit its development even at low doses [11]. However, the CECCY (Carvedilol Effect in Preventing Chemotherapy Induced Cardiotoxicity) trial randomized 200 patients with breast cancer, who were to receive anthracyclines (doxorubicin 240 mg / m^2), to receive either carvedilol therapy or placebo for primary prevention. At 6 months, no difference

was found (carvedilol cohort = 14.5% vs. placebo = 13.5%; $p = 1.0$) in the frequency of AIC between the groups [12].

M. Guglin et al. studied 468 women with HER2-positive breast cancer receiving trastuzumab. The women were randomized to receive treatment with lisinopril, carvedilol, or placebo. No significant difference was found in the primary endpoint of AIC development (32% in the placebo group, 29% in the carvedilol group, and 30% in the lisinopril group) [13].

ACE inhibitors, such as enalapril, are another group of drugs with an antioxidant effect considered for AIC treatment and prevention. It was found that in patients with increased risk of AIC, defined by elevated troponin I values, early treatment with enalapril could prevent the development and progression of late cardiotoxicity [14]. In another study that investigated enalapril and candesartan against placebo, enalapril appeared to decrease the LV end-systolic wall stress, although it did not improve the maximum cardiac index according to exercise echocardiography [15].

D. Cardinale et al. showed that patients who were randomized to receive enalapril for primary prevention had lower incidence of cardiac events compared with the control group ($p < 0.001$) [16]. The randomized OVERCOME (Prevention of Left Ventricular Dysfunction with Enalapril and Carvedilol in Patients Submitted to Intensive Chemotherapy for the Treatment of Malignant Hemopathies) trial showed that combination therapy prevented LVEF reduction compared with the control group at 6 months ($p = 0.035$), but there was no difference in serious adverse events between the groups [17].

Based on all of the above, enalapril and carvedilol are among the main drugs for AIC treatment that appear effective in reducing the incidence rates of left ventricular systolic dysfunction and preventing reduction of LVEF in patients with AIC [2, 5]. However, not all patients respond to therapy with these drugs. There are responders that have an increase in LVEF after therapy initiation and non-responders in whom LVEF does not increase, but sometimes even decreases, despite optimal drug therapy [6]. Authors point out several reasons why some patients may not respond to therapy. Firstly, it may depend on the irreversibility of damage in AIC. Early type I toxicity is often reversible, late type II toxicity involves an injury cascade that leads to almost irreversible changes [3]. Since most studies include patients with early AIC, the benefits of carvedilol and enalapril for patients with type II AIC have not been established yet [12–14, 17]. Secondly, genetic factors may be crucial in a patient's response to treatment and may help identify a subset of HP patients with AIC who might benefit from personalized intensification and optimization of treatment in order to reduce the development of adverse cardiovascular events [7, 18].

This study assessed the impact of genetic factors (polymorphisms in the *ADRB1* gene (Arg389Gly, rs1801253) and *ACE* gene (I/D, rs4343)) on the effectiveness of β-blocker (carvedilol) and ACE inhibitor (enalapril) therapy in women with AIC and without prior cardiovascular diseases during a 12-month follow-up period. Beta-1 adrenergic receptors (AR) play a pivotal role in the regulation of the cardiovascular system. Changes in expression or properties of the beta-1 adrenoceptors may have phenotypic consequences affecting their cardiovascular or metabolic function or may contribute to the pathophysiology of disorders like hypertension, congestive HF, asthma or obesity [19]. Thus, assessing the beta-1 adrenoceptor genotype, may help predict responsiveness to β-blocker treatment in patients with ischemic HF: patients homozygous for the Arg389 beta-1-AR polymorphism should be good responders while patients homozygous for the Gly389 beta-1-AR polymorphism should be poor responders or non-responders [20, 21].

L.M. Baudhuin et al. showed that carriers of the G/G genotype should receive an increased dose of the drug to achieve a therapeutic effect in HF treatment [22]. Another study found no relationship between the genotypes of the Arg389Gly polymorphism in the *ADRB1* gene and the effectiveness of carvedilol therapy in 183 HF patients with ischemic or non-ischemic cardiomyopathy, and LVEF ≤ 35% [23]. The C/C genotype is associated with a significantly greater increase in LVEF during carvedilol therapy in patients with HF of non-ischemic etiology compared with the C/G or G/G genotypes in the *ADRB1* gene [24]. These differences in the pharmacogenetic efficacy of carvedilol in assessing the Arg389Gly polymorphism in the *ADRB1* gene in different studies indicate the need for further research. A combined assessment with the *CYP2D6* polymorphism, which affects the pharmacokinetic effects of the drug [25] and the dosage regimen of the drug, is also promising, even though R. Shihmanter et al. revealed that variations in the CYP2D6 genotype were not associated with a change in the carvedilol dose in HF patients [26].

In this study, we evaluated the impact of the Arg389Gly polymorphism in the *ADRB1* gene on the pharmacodynamic effects of carvedilol. Thus, women with the G/G genotype in the *ADRB1* gene (Arg389Gly, rs1801253) had the absolute benefit from carvedilol and enalapril therapies. In these patients, LVEF significantly ($p < 0.001$) increased by 10.7%; ESD and EDD decreased by 5.8 ($p < 0.001$) and 6.0% ($p < 0.001$), respectively; LA size decreased by 9.7% ($p < 0.001$), 6MWT distance increased by 4.7% ($p = 0.008$), and NT-proBNP levels decreased by 34.8% ($p < 0.001$). In patients with the C/C and C/G genotypes, HF progressed further, which was manifested through a decrease in LVEF and an increase in LV and LA dimensions. However, we found that patients with a further decrease in LVEF and progression of HF were rarely carriers of the G/G genotype, which does not contradict the literature data, according to which the G/G genotype is rare and may even be absent in the general population [27]. Therefore, there is a need for further observations regarding this genotype in patients with AIC.

In the general population, the *ACE* gene was found to be associated with cardiovascular diseases and multiple cardiovascular risk factors, although some studies did not reveal such associations [28]. Polymorphisms in the *ACE* gene are associated with a response to ACE inhibitor therapy, but researchers have not reached consensus as to which allele has a more pronounced effect. In this study, we established for the first time that women with the G/G genotype in the *ACE* gene (I/D, rs4343) benefited from carvedilol and enalapril therapies. In these patients, LVEF significantly ($p = 0.002$) increased by 7%, ESD and EDD decreased by 5.3 ($p = 0.007$) and 3.0% ($p = 0.038$), respectively; LA size decreased by 3.3% ($p = 0.012$), and NT-proBNP levels decreased by 20.4% ($p = 0.007$). Carriers of the A/A genotype had further progression of HF which manifested through a decrease in LVEF and an increase in LV dimensions, but NT-proBNP levels tended to decrease by 20% ($p = 0.052$). Echocardiography parameters in carriers of the A/G genotype in the *ACE* gene (I/D, rs4343) did not change, but NT-proBNP levels significantly decreased by 19.6% ($p < 0.001$), which was probably due to concomitant β-blocker therapy.

It should be noted that our data do not suggest that β -blocker and ACE inhibitor therapy should be withheld only when genetic analysis is not favorable. However, evaluating these genes may help identify a subset of HP patients with AIC and LV dysfunction who might benefit from personalized intensification and optimization of treatment in order to reduce the development of adverse cardiovascular events.

CONCLUSION

Our data suggest that evaluation of *ADRB1* (Arg389Gly, rs1801253) and *ACE* gene (I/D, rs4343) polymorphisms may be recommended prior to the initiation of AIC treatment in women without known history of CVDs to determine patients with AIC and left ventricular dysfunction who will benefit from intensification and optimization of treatment to reduce the development of adverse cardiovascular events. Carriers of the G/G genotypes in the *ADRB1* and *ACE* genes (I/D, rs4343) benefited from carvedilol and enalapril therapy.

RESEARCH LIMITATIONS

The main limitations of the study included the small sample of patients, short-term follow-up, and the absence of hard endpoints. Further studies are required to clarify the role of the *ADRB1* (Arg389Gly, rs1801253) and *ACE* genes (I/D, rs4343) in assessing the effectiveness of beta-adrenoceptor (carvedilol) and ACE inhibitor (enalapril) therapy in women with AIC.

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