

## Association of the ABCB1 C3435T gene polymorphism (SNPs) with the response to neoadjuvant chemotherapy in women with breast cancer in northeastern Brazil

Associação do polimorfismo (SNPs) do gene ABCB1 C3435T, com a resposta à quimioterapia neoadjuvante, em mulheres com câncer de mama do Nordeste do Brasil.

Diego de Aragão Bezerra<sup>1</sup>, José Juvenal Linhares<sup>2\*</sup>, Emmanuelle Coelho Noronha<sup>3</sup>, Kaio César Simiano Tavares<sup>4</sup>, André Saraiva Leão Marcelo Antunes<sup>5</sup>, Regina Freitas Coelho<sup>6</sup>, Marcos Vinícius Souza Marques<sup>6</sup>

<sup>1</sup>Professor Assistente de Oncologia do Curso de Medicina Universidade Federal do Ceará-Campus de Sobral, <sup>2</sup>Professor Adjunto de Ginecologia e Obstetrícia do Curso de Medicina Universidade Federal do Ceará-Campus de Sobral, <sup>3</sup>Professor Assistente de Imunologia do Curso de Medicina Universidade Federal do Ceará-Campus de Sobral, <sup>4</sup>Coordenador do Núcleo de Biologia Experimental da Universidade de Fortaleza, <sup>5</sup>Pesquisador do Núcleo de Biologia Experimental da Universidade de Fortaleza, <sup>6</sup>Acadêmico de Medicina.

### Abstract

**Introduction:** breast cancer (BC) is the most common tumor and the leading cause of cancer-related death among the female population worldwide. Polymorphisms genetics of ABCB1 gene contributed to breast cancer susceptibility and interindividual differences in chemotherapy response. **Objectives:** to evaluate the association between the ABCB1 C3435T gene polymorphism (SNPs) with the response to neoadjuvant chemotherapy in women with breast cancer. **Methodology:** this study included 32 female patients who received neoadjuvant chemotherapy. The polymorphisms were genotyped through real-time allele-specific polymerase chain reaction (PCR). The statistical analysis was performed using the Fisher's exact test or Pearson's chi-square test in the Statistical Package for Social Sciences (SPSS) version 20.0 software. **Results:** the genotypes found for the C3435T polymorphism were in Hardy-Weinberg equilibrium and their genotypic distributions were CC= 10 (31.1%), CT= 14 (43.8%), and TT= 08 (25.0%) with  $\chi^2$ : 0.86 and p-value > 0.05. Allele frequencies were C = 0.54 and T = 0.46. There were no significant statistical differences between genotypes considering the response to neoadjuvant chemotherapy and immunohistochemistry; the presence of the T allele was associated with worsen axillary status response to neoadjuvant chemotherapy. **Conclusion:** no definite association between the presence of C3435T polymorphism and the response to neoadjuvant chemotherapy was observed. Further studies in Brazil involving larger samples will contribute to validating the results of this study.

**Keywords:** Breast cancer. Drug Therapy. Polymorphisms.

### Resumo

**Introdução:** o câncer de mama (CM) é o tumor mais comum e a principal causa de morte relacionada ao câncer na população feminina em todo o mundo. Polimorfismos genéticos do gene ABCB1 contribuem para a suscetibilidade ao câncer de mama e diferenças interindividuais na resposta à quimioterapia. **Objetivos:** avaliar a associação entre o polimorfismo (SNPs) do gene ABCB1 C3435T com a resposta à quimioterapia neoadjuvante em mulheres com câncer de mama. **Metodologia:** estudo com 32 pacientes do sexo feminino, que utilizaram quimioterapia neoadjuvante. A genotipagem dos polimorfismos foi feita por reação da polimerase em cadeia (PCR) em tempo real alelo específica. A análise estatística foi realizada mediante o teste exato de Fisher ou Qui-quadrado de Pearson, utilizando o software SPSS (Statistical Package for the Social Sciences) vs20.0. **Resultados:** os genótipos encontrados para o polimorfismo C3435T estavam em equilíbrio de Hardy-Weinberg e suas distribuições genotípicas foram respectivamente CC= 10 (31,1%), CT= 14 (43,8%), TT= 08 (25,0%) sendo,  $\chi^2$ : 0.86 e p-value > 0,05. As frequências alélicas foram de C= 0,54 e T= 0,46. Não ocorreram diferenças estatísticas entre os genótipos, considerando a resposta a quimioterapia neoadjuvante e a imunohistoquímica, sendo a presença do alelo T associada a pior resposta do status axilar à quimioterapia neoadjuvante. **Conclusão:** não foi possível correlacionar a presença do polimorfismo C3435T com a resposta à quimioterapia neoadjuvante, sendo necessária a realização de novos estudos no Brasil envolvendo casuísticas maiores para a validação dos resultados.

**Palavras-chave:** Câncer de mama. Quimioterapia. Polimorfismos.

### INTRODUCTION

Breast cancer (BC) is the most common tumor and the leading cause of cancer-related death among the female population worldwide (BRAY et al., 2018).

Locally advanced breast cancer (LABC) represents a heterogeneous group of diseases associated with poor prognosis. According to the TNM staging system from the

**Correspondente/Corresponding:** \*José Juvenal Linhares – End: Rua das Orquídeas, 60 Bairro: N.S de Fátima Sobral-CE CEP: 62034-122 – Tel: (88) 99922-3776 – E-mail: juvenallinhares@gmail.com

International Union Against Cancer (UICC)/American Joint Cancer Committee (AJCC), primary BC with extension to the skin, chest wall or inflammatory carcinoma, with or without lymph node involvement, and without metastasis can be included in stage III and considered a LABC (SINGLETARY et al., 2002).

Several studies are being conducted on the pharmacogenomics of antineoplastic chemotherapy drugs to reduce the dose and minimize undesirable effects by individualizing treatment. Neoadjuvant chemotherapy (NAC) is one of the most widely used forms of treatment for its effectiveness in certain potentially lethal neoplasms such as those in the breast, especially in patients with LABC (CICCOLINI et al., 2015).

NAC is a systemic therapy given before surgery to minimize the extent of surgery, reducing tumor size, and facilitating a conservative breast approach (AKHTAR et al., 2015). Researches had shown a significant increase in pathological response in primary BC patients when docetaxel was administered as the sequential therapy to doxorubicin and cyclophosphamide in a neoadjuvant scenario (RASTOGI et al., 2008). Randomized studies showed similar NAC responses compared to adjuvant therapy, encouraging the use of docetaxel in neoadjuvant settings (ASSELAIN et al., 2018). NAC followed by surgery, and adjuvant radiotherapy is the standard treatment for LABC patients (NCCN CLINICAL PRACTICE GUIDELINES IN ONCOLOGY, 2017).

However, the frequency of tumor regression shows rates ranging from 10 to 50%, and up to complete pathological response, however, NAC is ineffective in a large number of patients (KAUFMANN et al., 2012). The reasons for this heterogeneity may be due to genetic and non-genetic factors (NOGUCHI, 2006).

Genetic factors may influence the therapeutic efficacy and interfere with the survival of patients with BC, even those at similar clinical stages. Therefore, the availability of new biomarkers that can more accurately predict prognosis and treatment response is a central issue for improving therapeutic strategies (PHARMGKB. TAXANE PATHWAY, 2016).

ABCB1, the multi-drug resistance (MDR) gene, is responsible for reducing intracellular drug levels by the ATP-dependent efflux. The main factors leading to simultaneous resistance to various drugs are drug expulsion after entering the plasma membrane via efflux pumps, reduced uptake, altered target enzymes, altered drug metabolism, increased DNA repair, or failure of regulatory mechanisms of programmed cell death (apoptosis). One of these mechanisms is through host efflux pumps, and among them, the P-glycoprotein (P-gp) which is involved in the chemotherapy drug resistance presented by tumor cells (JABIR, et al., 2012, FLETCHER et al., 2010).

Because the current knowledge in this field is inconsistent and sometimes conflicting, further studies are needed to confirm the clinical importance of single gene nucleotide polymorphisms (SNPs) encoding these multidrug

resistance enzymes (MITTAL; TULSYAN; MITTAL, 2016).

This is the first study carried out with the primary objective of evaluating the association between the ABCB1 rs1045642 (C3435T) gene polymorphism and the response to NAC in patients with BC in Northeastern Brazil.

#### OBJECTIVES

To evaluate the association between the ABCB1 C3435T gene polymorphism (SNPs) and the response to NAC in women with BC.

#### METHODOLOGY

##### Study Design

This was an observational and prospective study in women with histopathological diagnosis of BC at clinical stage III, without previous treatment, and submitted to NAC. These patients were assisted at the Mastology Service of the Teaching Hospital of the Federal University of Ceará-Campus Sobral – Santa Casa de Misericórdia of Sobral and Ambulatory of the Center of Medical Specialties (CEM) of the Health Secretary of the city of Sobral – CE.

##### Sampling

DNA samples were extracted from 32 consecutive patients with LABC (clinical stage III). The cases were assessed between July of 2017 and July of 2018; patients were evaluated by physical examination and mammography, and the stage was confirmed by thick needle biopsies. All patients completed platinum and docetaxel-based NAC, surgery, radiotherapy, and hormone therapy when indicated. The response to chemotherapy was performed by the pathological analysis of the surgical specimen and clinically and radiologically after the last NAC cycle. Tumor response was assessed according to the RECIST criteria (Response Evaluation Criteria in Solid Tumor), using reports from physical examination and mammographic images performed before the beginning of the first cycle and after the completion of all docetaxel cycles, and the histopathological report from the surgical specimen (EISENHAUER et al., 2009). Eisenhauer et al. (2009) according to the RECIST criteria, the complete response (CR) represented the disappearance of all lesions assessed by the histopathological examination of the surgical specimen; the partial response (PR) represented  $\geq 30\%$  reduction in the sum of the largest diameters compared with those in the first examination (baseline); and progressive disease (PD) represented an increase in  $\geq 20\%$  in the sum of the largest diameters compared to the smallest sum recorded (not necessarily the baseline). The stable disease (SD) status does not fit into progression or response (EISENHAUER et al., 2009).

The exclusion criteria were intolerance to NAC, which prevented the completion of treatment, pregnancy, male gender, and metastatic or bilateral disease.

The study was approved by the Research Ethics Committee of the Federal University of Ceará (CAAE number:

78756016.5.0000.5054 and Opinion Number: 2,348,336). The informed consent form was signed, allowing the use of tissue samples in molecular analyses by all study participants prior to the study start.

## Genetic Analysis

### DNA Extraction

DNA was extracted by scraping the oral mucosa with a cytobrush according to the GFX<sup>®</sup> Cell, Tissue, and Blood Kit protocol (Amersham-Pharmacia<sup>®</sup>). DNA samples were used to perform the polymerase chain reaction (PCR-real time) to obtain the 249 bp fraction that includes the C3435T polymorphic region located on exon 26; the 5'-ATG GCC TCC GAG CAC sense primers and ACC TG-3' and 5'-AGG CAG TGA CTC GAT GAA GGC-3' antisense primers were used (Invitrogen<sup>™</sup> Life Technologies, Carlsbad, CA<sup>®</sup>) in an Eppendorf PCR thermocycler (Eppendorf GAC 22331, Hamburg, Germany<sup>®</sup>). The functional variants of the ABCB1 gene (c.3435C> T / rs1045642) were the CC genotype considered as a reference for comparisons with the CT (heterozygote) and TT (homozygote) variants. Genotyping was performed using the TaqMan<sup>®</sup> SNP assay (Applied Biosystems<sup>®</sup>, ID: C\_7586657\_20). Between 1 and 20 ng of DNA was used in PCR reactions performed in triplicates at the final volume of 20 µl using the ABI 7500 real-time PCR detection system (Applied Biosystems<sup>®</sup>). The cycling conditions were 50 °C for 2 min, 95 °C for 10 min; 40 cycles at 92 °C for 15 s; and pairing/extension at 60 °C for 1 min. Data were analyzed using the SDS v. 1.3.1<sup>®</sup> software.

### Statistical Analysis

Data were expressed as mean and standard deviation after categorization as absolute and percentage frequency and analyzed by the Fisher's exact test or Pearson's chi-square test.

The Fisher's exact or Chi-square association tests were used to evaluate the relationship of the tested genotypes (C3435T polymorphism genotypes) and the response to the neoadjuvant chemotherapy, and the lymph node response after therapy.

Analyzes were performed using the Statistical Package for the Social Sciences (SPSS)<sup>®</sup> software, version 20.0 for Windows, adopting a 95% confidence and p-value ≤ 0.05 as significant.

## RESULTS

The demographic characteristics, risk factors, and tumor characteristics of women with BC are described in Table 1.

**Table 1** – Demographic characteristics of the study population (N = 32).

Epidemiological data	N	%
<b>Age (51.56 ± 11.15)</b>		
Up to 50 years old	16	50.0
Over 50 years old	16	50.0
<b>Family history</b>		
No	20	62.5
Yes	12	37.5
<b>Smoking</b>		
No	25	78.1
Yes	7	21.9
<b>Menarche Age (13.23 ± 2.18)</b>		
Up to 12 years old	11	36.7
Over 12 years old	19	63.3
<b>Menopause Age (44.30 ± 6.26)</b>		
Up to 45 years old	13	48.1
Over 45 years old	14	51.9
<b>First childbirth age (20.61 ± 5.75)</b>		
Up to 20 years old	12	52.2
Between 21 and 30 years old	9	39.1
Over 30 years old	2	8.7
<b>Pregnancies (3.16 ± 1.49)</b>		
1	4	16.0
2 to 3	11	44.0
> 3	10	
<b>Hormone receptors</b>		
Negative	5	15.6
Positive	27	84.4
<b>HER2</b>		
Negative	12	44.4
Positive	10	62.5
<b>ki67 (31.07 ± 26.26)</b>		
< 15%	10	31.3
> 15%	22	68.8
<b>Response to NAC</b>		
Partial	28	87.5
Complete	4	12.5

Data are expressed in average ± SD

Fonte: dados da pesquisa

The genotypic distribution showed 10 (31.2%) as homozygous (CC), 08 (25%) as homozygous (TT), and 14 (43.8%) as heterozygous (CT).

No association between the presence of the C allele and response to NAC was observed, nor its association with the lymph node status, hormone receptors, HER-2, and KI-67 (Table 2).

**Table 2** – Association between the ABCB1 rs1045642 (C3435T) SNP genotype and the NAC response (C/T + CC vs. TT).

	Genotype				p-value*	OR	CI 95%	
	CT + CC		TT					
<b>NAC Response</b>								
Partial	21	87.5%	7	87.5%	1.000	1.00	0.09	11.24
Complete	3	12.5%	1	12.5%		1		
<b>Post NAC lymph node response</b>								
Negative	7	29.2%	4	50.0%	0.397	0.41	0.08	2.13
Positive	17	70.8%	4	50.0%		1		
<b>Hormone receptors</b>								
Negative	5	20.8%	0	0%	0.296	4.80	0.24	96.87
Positive	19	79,2%	8	100.0%		1		
<b>HER2</b>								
Negative	11	45.8%	1	12.5%	0.204	5,92	0.63	55.88
Positive	13	54.2%	7	87.5%		1		
<b>ki 67</b>								
< 15	8	33.3%	2	25.0%	1.000	1.50	0.25	9.18
> 15	16	66.7%	6	75%		1		

\* $p \leq 0.05$  was considered significant.

Fonte: dados da pesquisa

Table 3 shows that, when assessing the association of the T allele with the NAC response, a significant difference was observed about the lymph node status after NAC, however, without association with tumor size reduction or immunohistochemical markers.

**Table 3** – Association between the ABCB1 rs 1045642 (C3435T) SNP genotype and the NAC response (CT + TT vs. CC).

	Genotype				p-value*	OR	CI 95%	
	CT + TT		CC					
<b>NAC Response</b>								
Partial	20	90.9%	8	80.0%	0.387	2.50	0.30	20.92
Complete	2	9.1%	2	20.0%		1		
<b>Post NAC lymph node response</b>								
Negative	10*	45.5%	1	10.0%	<b>0.048</b>	<b>7.50</b>	<b>1.11</b>	<b>69.74</b>
Positive	12	54.5%	9th	90.0%		1		
<b>Hormone receptors</b>								
Negative	2	9.1%	3	30.0%	0.293	0.23	0.03	1.70
Positive	20	90.9%	7	70.0%		1		
<b>HER2</b>								
Negative	8	36.4%	4	40.0%	1.000	0.86	0.18	3.98
Positive	14	63.6%	6	60.0%		1		
<b>ki 67</b>								
< 15	7	31.8%	3	30.0%	1.000	1.09	0.21	5.52
> 15	15	68.2%	7	70.0%		1		

\* $p \leq 0.05$  was considered significant.

Fonte: dados da pesquisa

No statistical difference was observed in any of the studied variables when the association between the wild homozygote (CC) and the mutated (TT) genotype was evaluated (Table 4).

**Table 4** – Association of the ABCB1 rs1045642 (C3435T) SNP genotype with the NAC response (CC vs. TT).

	Genotype		CC	p-value*	OR	CI 95%		
	TT	CC						
<b>NACT Response</b>								
Partial	7	87.5%	8	80.0%	1.000	1.75	0.13	23.70
Complete	1	12.5%	2	20.0%		1		
<b>Post NAC lymph node response</b>								
Negative	4	50.0%	1	10.0%	0.118	9.00	0.75	108.31
Positive	4	50.0%	9	90.0%		1		
<b>Hormone receptors</b>								
Negative	0	0%	3	30.0%	0,216	0.13	0.01	2861.00
Positive	8	100.0%	7	70.0%		1		
<b>HER2</b>								
Negative	1	12.5%	4	40.0%	314	0.21	0.02	2.48
Positive	7	87.5%	6	60.0%				
<b>Ki 67</b>								
< 15	2	25.0%	3	30.0%	1.000	0.78	0.10	6.32
> 15	6	75%	7	70.0%		1		

\* $p \leq 0.05$  was considered significant.

Fonte: dados da pesquisa

## DISCUSSION

This study aimed to evaluate the association between the SNP polymorphism of the ABCB1-C3435T gene and the clinical response to NAC in women with breast cancer in northeastern Brazil.

We evaluated the action of this genetic polymorphism related to the multidrug resistance mechanism, where a complex phenomenon is observed, and contradictory results can be explained by gene-gene interactions. TT genotypes are involved in a defect in the p-glycoprotein production, which leads to drug accumulation within cells. However, other mechanisms may occur, resulting in resistance to chemotherapy. Other unknown polymorphisms in the MDR-1 gene and errors in the translation of the p-glycoprotein structural protein that may render it defective are observed in patients with the CC genotype (PRIYADARSHINI et al., 2019). We evaluated 32 patients with genotypes distributed as CC (31.2%), TC (43.8%), and TT (25%). These results are in agreement with those reported by Priyadarshini et al. (2019), in the southern Indian population with BC (n = 102) (PRIYADARSHINI et al., 2019). Madrid-paredes, et al. (2017), in a meta-analysis study, nine of the articles included studies on the ABCB1-C3435T gene polymorphism (770 patients), where the most prevalent genotype was CT; however, there were no South American studies in that analysis. Rodrigues et al. studied BC patients from southeastern Brazil and found distribution patterns similar to our results with 27.9% for CC, 52.2% for CT, and 20.3% for TT (RODRIGUES et al., 2008).

The association of the ABCB1-C3435T polymorphism and response in patients with BC treated with NAC was initially suggested in a study with 68 LABC patients where those who presented better clinical responses were TT

genotype carriers (OR: 4.38, 95% CI: 1.2-16.1,  $p = 0.029$ ) (KAFKA et al. 2003). In a meta-analysis study, nine articles involving the ABCB1-C3435T gene polymorphism (770 patients) indicated that the polymorphism was not associated with the NAC response in BC patients (MADRID-PAREDES et al. 2017, KAFKA et al. 2003). These results are similar to those in our study where we found no association between the SNP C3435T polymorphism of the MDR-1 gene and tumor response to NAC, hormone receptors, and HER-2 and Ki-67 expression.

Rodrigues et al. (2008) showed that the presence of the T allele was related to worse axillary status. The last study that mainly assessed axillary status was conducted in Brazil and showed discordant findings, i.e., no relationship between axillary involvement and the relationship between alleles; this discordance may be justified by the difference in sample and country region where the studies were conducted.

The present study is extremely important in the attempt to search for markers involved with the NAC response in women with BC, which could modify the treatment approach adopted for women with BC, especially within the Northeastern region of Brazil.

## CONCLUSION

The study shows that there was no statistical difference between the presence of C3435T polymorphism genotypes regarding the response to NAC; nevertheless, a worse response of axillary status was observed in the presence of the T allele. Further studies in Brazil involving larger samples will contribute to validating the results of this study.

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