RESEARCH ARTICLE

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# Influence of (C1236T and C3435T) Polymorphisms of *ABCB1* Gene on Chemotherapy Treatment Outcome and Toxicity in Breast Cancer Patients

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## Abstract

**Background:** ATP Binding Cassette Transporters (*ABCB1*) gene plays an important role in transport of different metabolites and anticancer drugs across the cell membrane. There is lack of knowledge on *ABCB1* gene polymorphism and its correlation with Adriamycin or paclitaxel based chemotherapy induced toxicity in breast cancer patients. Therefore in this study, we explored the correlation of *ABCB1* polymorphisms gene on response and toxicity in adriamycin and paclitaxel based chemotherapy in breast cancer patients from Indian population. **Methods:** Two hundred BC patients receiving Adriamycin and paclitaxel chemotherapy were enrolled in this study and chemotherapy induced hematological and non-hematological toxicity reactions were noted. The polymorphisms in *ABCB1* gene (C1236T, C3435T) were studied by PCR and RFLP analysis. **Results:** The univariate logistic regression analysis showed statistically significant negative association with protective effects of *ABCB1* (C3435T) polymorphism with heterozygous genotype (OR=0.34, 95% CI: 0.13-0.89; p=0.027), homozygous variant genotype (OR=0.31, 95% CI: 0.10-0.99; p=0.049) and combined C/T+T/T genotypes (OR=0.33, 95% CI: 0.13-0.79; p=0.013) in relation with severe toxicity of chemotherapy induced nausea and vomiting in breast cancer patients treated with Adriamycin chemotherapy. The 3435 C>T polymorphism of *ABCB1* gene with heterozygous C/T genotype showed significantly negative association (OR=0.37, 95% CI: 0.14-0.96; p=0.042) with peripheral neuropathy in patients treated primarily with paclitaxel thereafter Adriamycin. **Conclusion:** The findings obtained from this study revealed significant association of *ABCB1* 3435 C>T polymorphisms with non-hematological toxicity in response to adriamycin and paclitaxel based chemotherapy.

**Keywords:** Breast cancer- Genetic polymorphism- *ABCB1*- Chemotherapy- Toxicity

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## Introduction

Breast cancer (BC) is the leading cancer among women in India where 216 108 representing 13.5 % of new cases were reported in 2022 and expected to increase upto 232 832 in year 2025 [1]. Breast cancer is second most common cause of cancer causing deaths in India as compared to developed countries preliminarily because of lack of knowledge about the risk factors among women, delay in diagnosis, late presentation and inadequate treatment. The most common procedures for BC management are combination of surgery, radiotherapy, hormone therapy, chemotherapy or targeted therapy. Chemotherapy is a systemic adjuvant or neo-adjuvant therapywhere combination of anticancer drugs are administered intravenously through blood stream to kill cancer cells. The chemotherapeutic drugs can kill malignant cells along with harm the normal cells too. Almost all chemotherapy agents can cause severe aftereffects (acute toxicities) in patients treated with chemotherapy where haematological (Anaemia, neutropenia, febrile neutropenia, thrombocytopenia) and nonhematological (mucositis, chemotherapy induced nausea vomiting, fatigue, bodyache, peripheral neuropathy) adverse reactions are prominent [2-4]. The susceptibility of the BC patients towards chemotherapy is determined by genomic determinants which may be associated with the risk of chemotherapy induced toxicity. Genetic variations in the genes involved in different pathways such as DNA damage/repair, drug metabolism pathways including drug transporter and detoxification may be important components in determining or limiting the clinical outcomes and chemotherapy induced adverse effects [5, 6]. However, the patients carrying the genetic

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variants in genes that play a role in drug transport and metabolism and their role in drug toxicity profile is yet a subject of research.

The ATP binding cassette (ABC) transporters are the family of transmembrane proteins that helps in transporting different metabolites, carcinogens and anticancer drugs across the lipid extracellular and intracellular membranes [7]. *ABCB1* is an ABC transporter gene encodes permeability glycoprotein concerned with ATP dependent efflux of metabolites and drugs. The altered expression or genetic variations of *ABCB1* gene is responsible for its association with diverse therapeutic response [8, 9]. *ABCB1* is highly polymorphic in nature, where 1236C>T, 2677G>T/A, and 3435C>T are the most commonly studied polymorphisms for their association with drug pharmacokinetics and chemotherapy dependent toxicity reactions [8, 10-12]. Several studies deduced the effective contribution of *ABCB1* gene polymorphisms in increased risk of cancer, treatment response and chemotherapy induced toxicity in different cancer patients [9, 13-20]. However, very limited information is available on polymorphisms of *ABCB1* gene and their role in either paclitaxel or Adriamycin related chemotherapy toxicities in breast or other cancers. To the best of our knowledge, no studies have been carried out from India, to investigate the Adriamycin or paclitaxel based chemotherapy induced toxicity reactions among breast cancer patients. Therefore, in order to endorse the effective association of the polymorphisms in *ABCB1* gene with breast cancer risk and its role in chemotherapy associated toxicities, we assessed the common genetic variants of *ABCB1* gene and their possible association with chemotherapy induced toxicity in breast cancer patients. The two common genetic variants of *ABCB1* gene C1236T and C3435T are addressed in this study for their involvement in chemotherapy induced toxicities in breast cancer patients in response to Adriamycin and paclitaxel drugs. To address this, we analysed genetic polymorphisms of *ABCB1* gene (C1236T and C3435T) from 200 BC patients receiving either Adriamycin or Paclitaxel chemotherapy and assessed their acute toxicities. Also, we investigated the association of polymorphisms of *ABCB1* gene with demographic and clinicopathological features of BC patients. This information will help to understand the factors associated with chemotherapy induced toxicity which is important in treatment planning and decision making.

## Materials and Methods

*Patient enrollment and Clinical data*

A total of two hundred (200) BC patients seeking treatment at Department of Oncology of Krishna Hospital & Medical Research Center, Karad were enrolled in this study based on predefined inclusion and exclusion criteria.

*Inclusion critera*

Patients with 27 to 78 years age range, histopathologically confirmed, no metastasis at diagnosis, clinically localised or locally advanced tumors according to standard staging system were included in this study. Patients diagnosed with BC who were planned to receive Adjuvant chemotherapy postoperatively with standard Adriamycin and Cyclophosphamide chemotherapy followed by Paclitaxel chemotherapy. Locally advanced BC patients receiving neoadjuvant chemotherapy for downstaging. Patients with metastatic breast cancer receiving palliative chemotherapy with any of the drugs mentioned.

*Exclusion criteria*

Male BC Patients, No pathological diagnosis, relapsed disease or metastasis, No associated co-morbidities, incomplete treatment taken, incomplete follow-up, missing or incomplete data, Patients with abnormal renal or liver function tests at the time of enrollment. Patients with performance score of ECOG ≥2 were excluded from the study. The detailed clinic-pathological and demographic characteristics and follow-up information of the patients was recorded in predefined proforma and depicted in Table 1. After initiating chemotherapy treatment, the BC patients are followed up at regular intervals to assess the clinical response and acute toxicity reactions. The patients were communicated regarding the purpose of their involvement in the study protocol. Informed written consent was obtained from all patients. The study protocol was approved by Institutional Ethics Committee of Krishna Institute of Medical Sciences.

*Chemotherapy Treatment Regimen*

Once the patient was enrolled in to the study after fulfilling inclusion and exclusion criteria,written iformed consent was taken and chemotherapy was planned as per the stage of the patient. Patients received 4 cycles of combination chemotherapy with Adriamycin and Cyclophsphamide , followed by 4 cycles of 3 weekly Paclitaxel. After receiving 1st cycle of chemotherapy in each schedule, patient was followed again between Day10 to Day14 postchemotherapy for assessing chemotherapy related toxicities. Patient was explained regarding possible adverse effects and advised to report back in case of serious side effects or report during scheduled followup and details were noted and graded as per National Cancer Institute- Common Toxicity Criteria (NCI-CTC) 4.03 criteria. Additionally patients with locally advanced BC receiving neoadjuvant chemotherapy were assessed for response at the end of planned Adriamycin and Cyclophosphamide chemotherapy and again at end of Paclitaxel chemotherapy.

*Follow-up and toxicity assessment*

The BC patients treated with adjuvant and neo-adjuvant chemotherapy were followed up for 1year at the regular intervals for the assessment of treatment response and toxicity evaluation. The patients were routinely tested for blood and urine before each chemotherapy cycle to monitor health and to check chemotherapy induced after effects. The chemotherapy induced hematological and non-hematological toxicities were recorded and classified according to NCI-CTC Criteria. The hematological toxicities including anemia, neutropenia, thrombocytopenia and non-hematological toxicities such

as mucositis, chemotherapy induced nausea/vomiting (CINV), fatigue, bodyache, peripheral neuropathy were graded as 0, 1, 2, 3, 4. Both the hematological and non-hematological toxicities were documented and evaluated for their association with genetic polymorphisms of drug transporter genes. For comparison of BC patients with toxicity reactions (>1 grade) were considered as chemo-sensitive groups were compared to patients with ≤ 1 grade reactions.

*Sample collection and Genomic DNA isolation*

Five milliliter (mL) of whole blood from patients was collected in sterile EDTA containing vacutainer after receiving informed consent. Genomic DNA extraction was carried out from the peripheral blood sample using HipurA®Blood genomic DNA miniprep purification kit. (Cat no. MB504-250PR) (HiMedia Laboratories) following the manufacturer's instructions. This genomic DNA was used for genotyping assays.

*Genotyping assays*

The genotyping of *ABCB1* with was performed by polymerase chain reaction- restriction fragment length polymorphisms (PCR-RFLP). The PCR amplification for confirmation of *ABCB1* polymorphisms was carried out separately in 20 micro liter (µL) reaction mixtures containing 1X PCR buffer 0.2 mM each dNTP, 10 picomole (pmol) of each primers (IDT technologies) , 1U Taq DNApolymerase (GeNei, Merck Bioscience) and 100 nanogram (ng) of purified genomic DNA. The primer sequence used to amplify the *ABCB1* (C1236T and C3435T) polymorphisms are shown in Table 1. The PCR conditions for amplification of 272 bp fragment of C1236T polymorphism of *ABCB1*: Initial denaturation at 95°C for 5 minutes (min) followed by 30 cycles of 95°C- 30 seconds (sec) , 55°C- 30 sec, 72°C- 30 sec and final extension at 72°C for 10 min. The conditions for C3435T of 244 bp: Initial denaturation at 95°C for 5 min followed by 30 cyclesof 95°C- 30 sec, 60°C- 30 sec, 72°C- 30 sec and final extension at 72°C- 10 min. The PCR amplicons were subjected to restriction digestion using restriction enzymes with digestion conditions are detailed in Table 1. The PCR products and restriction digestion reactions were checked by agarose gel electrophoresis in Tris-Acetate-EDTA (TAE) buffer thereafter stained with ethidium bromide (10 mg/mL) and visualized under UV-transilluminator and photographed in gel documentation system (BioRad Laboratories).

*Statistical Analysis*

The genotype frequencies for each polymorphism and severity of both haematological and non-hematological toxicities were calculated. The association of each polymorphism and severity of toxicities were compared with clinico-pathological and demographic information of the patients by means of a Chi-square test. A univariate logistic regression model was used to assess the effect of the clinic-pathological variables, on incidence of toxicity (0-1 grade vs. 2-4), expressing results as Odds ratios (OR) and relative 95% confidence intervals (95% CIs). OR estimated to test whether any association exists between

Table 1. The List of Candidate *ABCB* Genes Selected in the Present Study with Details of PCR and RFLP Procedures Including Primers and Restriction Enzymes and Expected Products of Selected Genes.

| Gene/Genotype | rs number | Amino acid/ nucleotide change | Primer Sequence Forward/Reverse | PCR product size | Enzyme / Digestion conditions | Dominant (Wild type) | Heterozygous | Recessive (Mutant) |
|---|---|---|---|---|---|---|---|---|
| *ABCB1**8 exon-12 (C1236T) | rs1128503 | Gly412Gly (C>T) | FP: 5' - CTC GAA AAG AAG TTA AGG TAC A -3' RP: 5'- ATC TCA CCA TCC CCT CTG TG -3' | 272 bp | HaeIII 37°C for 16h | 250 bp 22 bp | 272bp, 250bp | 272 bp |
| *ABCB1**6 Exon-26 (C3435T) | rs1045642 | Ile1145Ile (C>T) | FP: 5'- TTG ATG GCA,AAG AAA TAA AGC -3' RP: 5'-CTT ACA TTA GGC AGT GAC TCG -3' | 244 bp | MboI 37°C for 16h | 175 bp 69 bp | 244 bp 175 bp | 244 bp |

the grade <1 toxicity caused by chemotherapy and selected gene polymorphisms. Statistical significance was set at $p < 0.05$. All statistical analyses were carried out using SPSS (Version 21.0).

## Results

*Demographic and Clinical characteristics of study population*

Two hundred (200) patients were enrolled in this study with age distribution ranging from 27-78 years with average age of 50.24 years. Out of 200 BC patients, 157 patients were >40 years with 122 women of ≤ 25 BMI whereas 78 women were > 25 BMI. The dietary habit of the women population is mixed with both vegetarian and non-vegetarian food. Out of 200, 130 women enrolled in this study were illiterate who did not attend school education because of poor economic status. 109 patients were tobacco users. 155 women were treated with adjuvant chemotherapy, 31 patients were treated eith neo-adjuvant chemotherapy and 14 patients were administered palliative chemotherapy. Out of 200 patients 81 patients were treated in combination with adjuvant radiotherapy. When hormone receptor status of the patients was diagnosed by immunohistochemistry, 83 patients were ER/PR positive, and 109 patients showed ER/PR negative and 85 patients were triple negative status. The tumor size of 95 patients was >2 centimeter (Range 2-10 cm), and 105 patients showed ≤ 2cm tumor size. Out of 200 patients, 98 patients showed clinical TNM stage of III and IV and 110 patients showed histopathological TNM stage of III and IV. 104 patients were first administered with Adriamycin followed by paclitaxel chemotherapy where as 96 patients were first treated with paclitaxel and then Adriamycin.

*Genotype distribution of ABCB1 gene (C1236T, C3435T) polymorphisms and chemotherapy toxicity in BC patients*

The univariate analysis of drug transporter *ABCB1*) gene polymorphism and its association with Adriamycin chemotherapy induced severe toxicity of hematological and non-hematological reactions are presented in Table 2 and Table 3. The hematological (anemia, neutropenia, febrile neutrepenia, thrombocytopenia) and non-hematological toxicities (mucositis, CINV, Fatigue, body ache, peripheral neuropathy) were graded into grade ≤1 or >1 toxicities based on NCI-CTC criteria. Out of 200 BC patients, 104 patients were primarily treated with Adriamycin thereafter paclitaxel out of which 23 patients showed severe grade toxicity (grade >1) anemia, 25 patients with severe neutropenia 24 patients with febrile neutropenia and only 7 patients showed severe thrombocytopenia.The severe non-hematological toxicities with grade >1 were observed with mucositis in 16 patients, CINV in 34 patients, fatigue in 37 patients, badyache in 15 patients and peripheral neuropathy in 5 patients after treatment with adriamycin chemotherapy. The univariate logistic regression analysis of genetic polymorphism in ABCB 1 gene with C1236T and C3435T genotypes did not show any significant association with hematological toxicity reactions including either anemia, neutropenia or thrombocytopenia in BC patients treated with Adriamycin chemotherapy (Table 2). The univariate logistic regression analysis showed statistically significant negative association with protective effects of *ABCB1* (C3435T) polymorphism with heterozygous genotype (OR=0.34, 95% CI: 0.13-0.89; p=0.027), homozygous variant genotype (OR=0.31, 95% CI: 0.10-0.99; p=0.049) and combined C/T+T/T genotypes (OR=0.33, 95% CI: 0.13-0.79; p=0.013) in relation with severe toxicity of chemotherapy induced nausea and vomiting in BC patients treated with Adriamycin chemotherapy. The non-hematological toxicities in response to Adriamycin chemotherapy and distribution of *ABCB1* (C1236T, C3435T) genotypes are represented in Table 3. The polymorphic C1236T and C3435T genotypes of *ABCB1* gene did not show any significant association with mucositis, fatigue, body ache, peripheral neuropathy in response to Adriamycin. Similarly, the associations between the genetic polymorphisms of *ABCB1* gene with C1236T and C3435T with severe hematological and non-hematological toxicity reaction in patients treated with paclitaxel chemotherapy are studied. The logistic regression analysis showed that neither C1236T nor C3435T polymorphism of *ABCB1* gene showed any association with hematological toxicities anemia, neutropenia or thrombocytopenia (Table 4). Similarly C1236T polymorphism of *ABCB1* gene was not associated with any of non-hematological toxicities such as mucositis, CINV, Body ache, peripheral neuropathy (Table 5). The C3435T polymorphism of *ABCB1* gene with heterozygous C/T genotype showed significant negative association (OR=0.37, 95% CI: 0.14-0.96; p=0.042) with peripheral neuropathy in patients treated primarily with paclitaxel thereafter Adriamycin. There was no difference observed when severe toxicity of mucositis, CINV, fatigue and body ache in patients with C3435T genotype treated with paclitaxel and Adriamycin.

*Association of ABCB1 (C1236T, C3435T) polymorphisms with demographic and clinicopathological factors of BC patients*

The association between genetic polymorphisms of *ABCB1* gene and the patients demographic and clinicopathological features is presented in Table 6. The demographic factors including age and body mass index of BC patients enrolled in this study did not show any significant association with polymorphism of C1236T or C3435T genotypes of *ABCB1* gene. The univariate logistic regression analysis showed no association of *ABCB1* genotypes with clinicopathological factors of BC patients. There was no statistically significant association among genotype distributions of *ABCB1* gene and hormone receptor (ER, PR and HER2) status in the studied population.

## Discussion

The chemotherapeutic drugs used in cancer treatment are implicated for their target specific mechanism of action; however, the knowledge on the mechanism of action of majority of chemotherapy drugs is inadequate.

Table 2. UnivariateAnalysis of Candidate SNPs of Drug Transporter (*ABCB1*) Gene and Risk of Chemotherapy (Adriamycin) Induced Severe Toxicity of Hematological Reactions in Breast Cancer Patients

| | | Anemia | | | |
|---|---|---|---|---|---|
| Gene Name SNP | Genotype | Grade ≤1 (n=81) | Grade >1 (n=23) | OR (95% CI) | p value |
| | C/C | 31 | 9 | 1 (Reference) | |
| *ABCB1* | C/T | 38 | 6 | 0.54 (0.17-1.69) | 0.293 |
| (rs1128503) | T/T | 12 | 8 | 2.29 (0.71-7.34) | 0.161 |
| | C/T+ T/T | 50 | 14 | 0.96 (0.37-2.49) | 0.94 |
| | C/C | 27 | 5 | 1 (Reference) | |
| *ABCB1* | C/T | 34 | 13 | 2.06 (0.65-6.51) | 0.216 |
| (rs1045642) | T/T | 20 | 5 | 1.35 (0.34-5.30) | 0.667 |
| | C/T + T/T | 54 | 17 | 1.70 (0.56-5.10) | 0.344 |
| | | Neutropenia | | | |
| Gene Name SNP | Genotype | Grade ≤1 (n=79) | Grade >1 (n=25) | OR (95% CI) | p value |
| | C/C | 29 | 11 | 1 (Reference) | |
| *ABCB1* | C/T | 36 | 8 | 0.58 (0.20-1.64) | 0.31 |
| (rs1128503) | T/T | 14 | 6 | 1.12 (0.34-3.68) | 0.839 |
| | C/T+ T/T | 50 | 14 | 0.73 (0.29-1.83) | 0.514 |
| | C/C | 24 | 8 | 1 (Reference) | |
| *ABCB1* | C/T | 33 | 14 | 1.27 (0.46-3.51) | 0.641 |
| (rs1045642) | T/T | 22 | 3 | 0.40 (0.09-1.73) | 0.226 |
| | C/T + T/T | 55 | 17 | 0.92 (0.35-2.44) | 0.878 |
| | | Febrile Neutropenia | | | |
| Gene Name SNP | Genotype | Grade ≤1 (n=80) | Grade >1 (n=24) | OR (95% CI) | p value |
| | C/C | 29 | 11 | 1 (Reference) | |
| *ABCB1* | C/T | 36 | 8 | 0.58 (0.20-1.64) | 0.31 |
| (rs1128503) | T/T | 15 | 5 | 0.87 (0.25-2.99) | 0.836 |
| | C/T+ T/T | 56 | 13 | 0.61 (0.24-1.53) | 0.295 |
| | C/C | 26 | 6 | 1 (Reference) | |
| *ABCB1* | C/T | 33 | 14 | 1.83 (0.62-5.44) | 0.271 |
| (rs1045642) | T/T | 21 | 4 | 0.82 (0.20-3.31) | 0.786 |
| | C/T + T/T | 54 | 18 | 1.44 (0.51-4.06) | 0.486 |
| | | Thrombocytopenia | | | |
| Gene Name SNP | Genotype | Grade ≤1 (n=97) | Grade >1 (n=7) | OR (95% CI) | p value |
| | C/C | 38 | 2 | 1 (Reference) | |
| *ABCB1* | C/T | 42 | 2 | 0.90 (0.12-6.74) | 0.922 |
| (rs1128503) | T/T | 17 | 3 | 3.35 (0.51-21.93) | 0.206 |
| | C/T+ T/T | 59 | 5 | 1.61 (0.29-8.72) | 0.58 |
| | C/C | 31 | 1 | 1 (Reference) | |
| *ABCB1* | C/T | 42 | 5 | 3.69 (0.41-33.19) | 0.244 |
| (rs1045642) | T/T | 24 | 1 | 1.29 (0.07-21.72) | 0.858 |
| | C/T + T/T | 66 | 6 | 2.81 (0.32-24.42) | 0.347 |

SNP, Single nucleotide polymorphism; OR, Odds ratio; CI, Confidence interval; Significance $p< 0.05$; *, Indicates significant Odds Ratio ($p<0.05$), p value determined based on $\chi^2$

*ABCB1* gene is important drug transporter and known for its role in absorption and disposition of chemotherapy drugs. Genetic polymorphisms in *ABCB1* gene can affect the pharmacokinetics of variety of drugs which may lead to altered drug efficacy, deviation in chemotherapy outcomes and adverse side effects of chemotherapy drugs.

Table 3. Univariate Analysis of Candidate SNPs of Drug Transporter (ABCB1) Gene and Risk of Chemotherapy (Adriamycin) Induced Non-Hematological Reactions in Breast Cancer Patients.

| Mucositis | | | | | |
|---|---|---|---|---|---|
| Gene Name SNP | Genotype | Grade ≤1 (n=88) | Grade >1 (n=16) | OR (95% CI) | p value |
| *ABCB1* | C/C | 32 | 8 | 1 (Reference) | |
| (rs1128503) | C/T | 39 | 5 | 0.51 (0.15-1.72) | 0.279 |
| | T/T | 17 | 3 | 0.70 (0.16-3.01) | 0.638 |
| | C/T+ T/T | 56 | 8 | 0.57 (0.19-1.66) | 0.306 |
| *ABCB1* | C/C | 29 | 3 | 1 (Reference) | |
| (rs1045642) | C/T | 38 | 9 | 2.28 (0.56-9.22) | 0.243 |
| | T/T | 21 | 4 | 1.84 (0.37-9.10) | 0.454 |
| | C/T+ T/T | 59 | 13 | 2.12 (0.56-8.06) | 0.265 |
| (CINV) | | | | | |
| Gene Name SNP | Genotype | Grade ≤1 (n=70) | Grade >1 (n=34) | OR (95% CI) | p value |
| *ABCB1* | C/C | 25 | 15 | 1 (Reference) | |
| (rs1128503) | C/T | 34 | 10 | 0.49 (0.18-1.27) | 0.142 |
| | T/T | 11 | 9 | 1.36 (0.45-4.05) | 0.576 |
| | C/T+ T/T | 45 | 19 | 0.70 (0.30-1.62) | 0.409 |
| *ABCB1* | C/C | 16 | 16 | 1 (Reference) | |
| (rs1045642) | C/T | 35 | 12 | 0.34 (0.13-0.89) | 0.027* |
| | T/T | 19 | 6 | 0.31 (0.10-0.99) | 0.049* |
| | C/T+ T/T | 54 | 18 | 0.33 (0.13-0.79) | 0.013* |
| Fatigue | | | | | |
| Gene Name SNP | Genotype | Grade ≤1 (n=67) | Grade >1 (n=37) | OR (95% CI) | p value |
| *ABCB1* | C/C | 28 | 12 | 1 (Reference) | |
| (rs1128503) | C/T | 30 | 14 | 1.08 (0.43-2.75) | 0.857 |
| | T/T | 9 | 11 | 2.85 (0.93-8.65) | 0.064 |
| | C/T+ T/T | 39 | 25 | 1.49 (0.64-3.47) | 0.348 |
| *ABCB1* | C/C | 19 | 13 | 1 (Reference) | |
| (rs1045642) | C/T | 30 | 17 | 0.82 (0.32-2.08) | 0.688 |
| | T/T | 18 | 7 | 0.56 (0.18-1.74) | 0.323 |
| | C/T+ T/T | 48 | 24 | 0.73 (0.30-1.72) | 0.474 |
| *ABCB1* | C/C | 36 | 4 | 1 (Reference) | |
| (rs1128503) | C/T | 38 | 6 | 1.42 (0.37-5.45) | 0.608 |
| | T/T | 15 | 5 | 3.00 (0.70-12.74) | 0.136 |
| | C/T+ T/T | 53 | 11 | 1.86 (0.55-6.32) | 0.315 |
| *ABCB1* | C/C | 27 | 5 | 1 (Reference) | |
| (rs1045642) | C/T | 39 | 8 | 1.10 (0.32-3.75) | 0.869 |
| | T/T | 23 | 2 | 0.46 (0.08-2.65) | 0.392 |
| | C/T+ T/T | 62 | 10 | 0.87 (0.27-2.79) | 0.816 |
| Peripheral neuropathy | | | | | |
| Gene Name SNP | Genotype | Grade ≤1 (n=99) | Grade >1 (n=5) | OR (95% CI) | p value |
| *ABCB1* | C/C | 39 | 1 | 1 (Reference) | |
| (rs1128503) | C/T | 43 | 1 | 0.90 (0.05-14.99) | 0.945 |
| | T/T | 17 | 3 | 6.88 (0.66-71.00) | 0.105 |
| | C/T+ T/T | 60 | 4 | 2.60 (0.28-24.13) | 0.4 |
| Peripheral neuropathy | | | | | |
| Gene Name SNP | Genotype | Grade ≤1 (n=99) | Grade >1 (n=5) | OR (95% CI) | p value |
| *ABCB1* | C/C | 31 | 1 | 1 (Reference) | |
| (rs1045642) | C/T | 43 | 4 | 2.88 (0.30-27.07) | 0.354 |
| | T/T | 25 | 0 | 0.41 (0.01-10.54) | 0.591 |
| | C/T+ T/T | 68 | 4 | 1.82 (0.19-16.99 | 0.597 |

SNP, Single nucleotide polymorphism; OR, Odds ratio; CI, Confidence interval; Significance p< 0.05; *, Indicates significant Odds Ratio (p<0.05), p value determined based on $\chi^2$

Table 4. Univariate Analysis of Candidate SNPs of Drug Transporter (*ABCB1*) Gene and Risk of Chemotherapy (Paclitaxel) Induced Severe Toxicity of Hematological Reactions in Breast Cancer Patients.

| | | Anemia | | | |
|---|---|---|---|---|---|
| Gene Name SNP | Genotype | Grade ≤1 (n=80) | Grade >1 (n=16) | OR (95% CI) | p value |
| | C/C | 32 | 4 | 1 (Reference) | |
| *ABCB1* | C/T | 32 | 8 | 2.00 (0.54-7.31) | 0.294 |
| (rs1128503) | T/T | 16 | 4 | 2.00 (0.44-9.05) | 0.368 |
| | C/T+ T/T | 48 | 12 | 2.00 (0.59-6.75) | 0.264 |
| | C/C | 30 | 5 | 1 (Reference) | |
| *ABCB1* | C/T | 34 | 8 | 1.41 (0.41-4.78) | 0.579 |
| (rs1045642) | T/T | 16 | 3 | 1.12 (0.23-5.32) | 0.882 |
| | C/T + T/T | 50 | 11 | 1.32 (0.41-4.16) | 0.636 |
| | | Neutropenia | | | |
| Gene Name SNP | Genotype | Grade ≤1 (n=81) | Grade >1 (n=15) | OR (95% CI) | p value |
| | C/C | 32 | 4 | 1 (Reference) | |
| *ABCB1* | C/T | 31 | 9 | 2.32 (0.64-8.33) | 0.195 |
| (rs1128503) | T/T | 18 | 2 | 0.88 (0.14-5.33) | 0.897 |
| | C/T+ T/T | 49 | 11 | 1.79 (0.52-6.13) | 0.35 |
| | C/C | 30 | 5 | 1 (Reference) | |
| *ABCB1* | C/T | 33 | 9 | 1.63 (0.49-5.43) | 0.421 |
| (rs1045642) | T/T | 18 | 1 | 0.33 (0.03-3.08) | 0.333 |
| | C/T + T/T | 51 | 10 | 1.17 (0.36-3.76) | 0.784 |
| | | Febrile Neutropenia | | | |
| Gene Name SNP | Genotype | Grade ≤1 (n=82) | Grade >1 (n=14) | OR (95% CI) | p value |
| | C/C | 32 | 4 | 1 (Reference) | |
| *ABCB1* | C/T | 33 | 7 | 1.69 (0.45-6.36) | 0.432 |
| (rs1128503) | T/T | 17 | 3 | 1.41 (0.28-7.05) | 0.674 |
| | C/T+ T/T | 50 | 10 | 1.60 (0.46-5.53) | 0.458 |
| | C/C | 30 | 5 | 1 (Reference) | |
| *ABCB1* | C/T | 34 | 8 | 1.41 (0.41-4.78) | 0.579 |
| (rs1045642) | T/T | 18 | 1 | 0.33 (0.03-3.08) | 0.333 |
| | C/T + T/T | 52 | 9 | 1.03 (0.31-3.38) | 0.95 |
| | | Thrombocytopenia | | | |
| Gene Name SNP | Genotype | Grade ≤1 (n=94) | Grade >1 (n=2) | OR (95% CI) | p value |
| | C/C | 35 | 1 | 1 (Reference) | |
| *ABCB1* | C/T | 40 | 0 | 0.29 (0.01-7.40) | 0.455 |
| (rs1128503) | T/T | 19 | 1 | 1.84 (0.10-31.13) | 0.672 |
| | C/T+ T/T | 59 | 1 | 0.59 (0.03-9.78) | 0.715 |
| | C/C | 34 | 1 | 1 (Reference) | |
| *ABCB1* | C/T | 41 | 1 | 0.82 (0.05-13.75) | 0.896 |
| (rs1045642) | T/T | 19 | 0 | 0.58 (0.02-15.18) | 0.75 |
| | C/T + T/T | 60 | 1 | 0.56 (0.03-9.35) | 0.691 |

SNP, Single nucleotide polymorphism; OR, Odds ratio; CI, Confidence interval; Significance p< 0.05; *, Indicates significant Odds Ratio (p<0.05); p value determined based on $\chi^2$

The *ABCB1* gene is highly polymorphic in nature where C1236T and C3435T polymorphisms are commonly studied in different population and different clinical settings with diverse distribution among different ethnic groups [8, 10-12, 21]. Earlier studies demonstrated that genetic variations of *ABCB1* gene are associated with

Table 5. Univariate Analysis of Candidate SNPs of Drug Transporter (*ABCB1*) Gene and Risk of Chemotherapy (Paclitaxel) Induced Non-Hematological Reactions in Breast Cancer Patients

| | | Mucositis | | | |
|---|---|---|---|---|---|
| Gene Name | Genotype | Grade ≤1 | Grade >1 | OR (95% CI) | p value |
| SNP | | (n=88) | (n=8) | | |
| *ABCB1* | C/C | 0.34 | 2 | 1 (Reference) | |
| (rs1128503) | C/T | 37 | 3 | 1.37 (0.21-8.75) | 0.733 |
| | T/T | 17 | 3 | 3.00 (0.45-19.69) | 0.252 |
| | C/T+ T/T | 54 | 6 | 1.88 (0.36-9.90) | 0.451 |
| *ABCB1* | C/C | 32 | 3 | 1 (Reference) | |
| (rs1045642) | C/T | 37 | 5 | 1.44 (0.31-6.50) | 0.634 |
| | T/T | 19 | 0 | 0.23 (0.01-4.85) | 0.351 |
| | C/T+ T/T | 56 | 5 | 0.95 (0.21-4.25) | 0.949 |
| | | (CINV) | | | |
| Gene Name | Genotype | Grade ≤1 | Grade >1 | OR (95% CI) | p value |
| SNP | | (n=66) | (n=30) | | |
| *ABCB1* | C/C | 25 | 11 | 1 (Reference) | |
| (rs1128503) | C/T | 28 | 12 | 0.97 (0.36-2.59) | 0.958 |
| | T/T | 13 | 7 | 1.22 (0.38-3.90) | 0.733 |
| | C/T+ T/T | 41 | 19 | 1.05 (0.43-2.57) | 0.909 |
| *ABCB1* | C/C | 24 | 11 | 1 (Reference) | |
| (rs1045642) | C/T | 29 | 13 | 0.97 (0.37-2.57) | 0.964 |
| | T/T | 13 | 6 | 1.00 (0.30-3.35) | 0.99 |
| | C/T+ T/T | 42 | 19 | 0.98 (0.40-2.41) | 0.977 |
| | | Fatigue | | | |
| Gene Name | Genotype | Grade ≤1 | Grade >1 | OR (95% CI) | p value |
| SNP | | (n=67) | (n=29) | | |
| *ABCB1* | C/C | 26 | 10 | 1 (Reference) | |
| (rs1128503) | C/T | 27 | 13 | 1.25 (0.46-3.35) | 0.654 |
| | T/T | 14 | 6 | 1.11 (0.33-3.70) | 0.86 |
| | C/T+ T/T | 41 | 19 | 1.20 (0.48-2.99) | 0.688 |
| *ABCB1* | C/C | 23 | 12 | 1 (Reference) | |
| (rs1045642) | C/T | 31 | 11 | 0.68 (0.25-1.81) | 0.44 |
| | T/T | 13 | 6 | 0.88 (0.26-2.91) | 0.84 |
| | C/T+ T/T | 44 | 17 | 0.74 (0.30-1.81) | 0.51 |
| | | Body ache | | | |
| Gene Name | Genotype | Grade ≤1 | Grade >1 | OR (95% CI) | p value |
| SNP | | (n=48) | (n=48) | | |
| *ABCB1* | C/C | 20 | 16 | 1 (Reference) | |
| (rs1128503) | C/T | 20 | 20 | 1.25 (0.60-3.08) | 0.628 |
| | T/T | 8 | 12 | 1.87 (0.61-5.69) | 0.267 |
| | C/T+ T/T | 28 | 32 | 1.42 (0.62-3.37) | 0.399 |
| *ABCB1* | C/C | 13 | 22 | 1 (Reference) | |
| (rs1045642) | C/T | 24 | 18 | 0.44 (0.17-1.11) | 0.082 |
| | T/T | 11 | 8 | 0.42 (0.13-1.34) | 0.146 |
| | C/T+ T/T | 35 | 26 | 0.43 (0.18-1.03) | 0.058 |
| | | Peripheral neuropathy | | | |
| Gene Name | Genotype | Grade ≤1 | Grade >1 | OR (95% CI) | p value |
| SNP | | (n=60) | (n=36) | | |
| *ABCB1* | C/C | 25 | 11 | 1 (Reference) | |
| (rs1128503) | C/T | 24 | 16 | 1.45 (0.56-3.77) | 0.441 |
| | T/T | 11 | 9 | 1.78 (0.57-5.54) | 0.316 |
| | C/T+ T/T | 35 | 25 | 1.55 (0.64-3.75) | 0.322 |
| *ABCB1* | C/C | 17 | 18 | 1 (Reference) | |
| (rs1045642) | C/T | 30 | 12 | 0.37 (0.14-0.96) | 0.042* |
| | T/T | 13 | 6 | 0.43 (0.13-1.40) | 0.165 |
| | C/T+ T/T | 43 | 18 | 0.39 (0.16-0.93) | 0.034* |

SNP, Single nucleotide polymorphism; OR, Odds ratio; CI, Confidence interval; Significance p< 0.05; *, Indicates significant Odds Ratio (p<0.05); p value determined based on $\chi^2$

Table 6. Polymorphisms of Drug Transporter Gene (*ABCB1*) and Their Association with Demographic and Clinicopathological Characterstics of Breast Cancer Patients

| Characteristics | *ABCB1* C1236T (rs1128503) | | *ABCB1* C3435T (rs1045642) | |
|---|---|---|---|---|
| | C/C No (%) | C/T/T/T No (%) | C/C No (%) | C/T/T/T No (%) |
| Age | | | | |
| ≤ 40 | 11 (5.50) | 32 (16.00) | 12 (6.00) | 31(15.50)) |
| >40 | 66 (33.00) | 91 (45.50) | 56 (28.00) | 101 (50.50) |
| OR (95% CI) | 1 Reference | 0.47 (0.22-1.08) | 1 Reference | 0.69 (0.33-0.46) |
| p value | | 0.053 | | 0.342 |
| BMI Kg/m$^2$ | | | | |
| ≤ 25 | 53 (26.50) | 69 (34.50) | 41(20.50) | 81(40.50) |
| >25 | 24(12.00) | 54 (27.00) | 27 (13.50) | 51(25.50) |
| OR (95% CI) | 1 Reference | 1.72 (0.94-3.14) | 1 Reference | 0.95 (0.52-1.74) |
| p value | | 0.073 | | 0.883 |
| Clinical TNM Grade | | | | |
| ≤ Stage II | 38 (19.00) | 64 (32.00) | 34 (17.00) | 68 (34.00) |
| > Stage II | 39 (19.50) | 59 (29.50) | 34 (17.00) | 64 (32.00) |
| OR (95% CI) | 1 Reference | 0.89 *0.50-1.58) | 1 Reference | 0.94 (0.52-1.68) |
| p value | | 0.712 | | 0.839 |
| Histopathological TNM Grade | | | | |
| ≤ Stage II | 32 (16.00) | 58 (29.00) | 31(15.50) | 59 (29.50) |
| > Stage II | 45 (22.50) | 65 (32.50) | 37 (18.50) | 73 (36.50) |
| OR (95% CI) | 1 Reference | 0.79 (0.44-1.41) | 1 Reference | 1.03 (0.57-1.86) |
| p value | | 0.439 | | 0.904 |
| Hormone receptor Status | | | | |
| ER/PR +ve | 36 (18.00) | 47(23.50) | 22 (11.00) | 61(30.50) |
| ER/PR -ve | 41 (20.50) | 76 (38.00) | 46 (46.00) | 71(35.50) |
| OR (95% CI) | 1 Reference | 1.41 (0.79-2.52) | 1 Reference | 0.55 (0.30-1.02) |
| p value | | 0.233 | | 0.06 |
| Her2 +ve | 16 (8.00) | 16 (8.00) | 7 (3.50) | 25 (12.50) |
| Her2 -ve | 61(30.50) | 107 (53.50) | 61 (30.50) | 107 (53.50) |
| OR (95% CI) | 1 Reference | | 1 Reference | 0.45 (0.18-1.10) |
| p value | 1.75 (0.81-3.75) | 0.147 | | 0.082 |

OR, Odds ratio; CI, Confidence interval; Significance p< 0.05; *, Indicates significant Odds Ratio (p<0.05), p value determined based on $\chi^2$

altered therapeutic response towards wide range of chemotherapy agents. Several reports demonstrated the effects of *ABCB1* polymorphisms with chemotherapy induced toxicities in BC patients [8, 11], however other studies proposed insignificant findings with conflicting outcomes where no association of 3435 C>T with hematological toxicities observed in BC patients [8, 22]. Similarly, 1236 C>T polymorphisms of *ABCB1* have demonstrated for their association with hematological toxicity in BC patients [8], however, same study denied significant association of 3435 C>T polymorphisms with hematological toxicity reactions in BC patients. Another study reported no association of 1236C>T polymorphism of *ABCB1* with chemotherapy drug induced severe toxicities [23]. Another studies on polymorphisms of *ABCB1* (1236 C>T and 3435 C>T) reported no association with hematologic toxicities in BC patients from Chinese population in response to cyclophosphamide and doxorubicin chemotherapy [10, 24].

Thus, number of studies revealed the outcomes of genetic association of *ABCB1* transporter gene polymorphisms with array of chemotherapy drugs in BC, however the literature information on Adriamycin and paclitaxel based chemotherapy and its toxicity outcomes in BC is missing. Therefore, it is essential to know effective role of polymorphisms of *ABCB1* drug transporters in chemotherapy response, drug toxicity and clinical outcomes of Adriamycin and paclitaxel based chemotherapy in BC patients. In this study, we examined the severity effects of Adriamycin and paclitaxel chemotherapy induced toxicities in BC patients and their plausible association with genetic variants of *ABCB1* gene and also clinic-pathological features among BC patients from rural population of India. The detailed

analysis of polymorphisms of *ABCB1* gene and its association with chemotherapy induced toxicity showed that the genotype frequencies of both heterozygous and homozygous variant genotypes of *ABCB1* C1236T were not statistically significant in any of the severe toxicities against Adriamycin or paclitaxel drugs. The *ABCB1*C3435T polymorphism of both heterozygous and homozygous variant genotypes showed negative significance with non-hematological toxicity reactions in BC patients in response to Adriamycin and paclitaxel. No significant linkage was observed between polymorphisms of either C1236T or C3435T of *ABCB1* and the incidence of anemia, neutropenia or thrombocytopenia ($p>0.05$). Our study is in agreement with other studies conducted by other researchers on BC treatment with paclitaxel chemotherapy showed no association between C1226T and C3435T polymorphism with neutropenia toxicity with grade >2 [25]. Similarly earlier reports also demonstrated the response of paclitaxel in gastric and ovarian cancer which produced neutropenia and neuropathy in patients with 3435 C>T polymorphisms of *ABCB1* gene [26, 27]. Other reports correlated the association of polymorphisms of 3435 C>T of *ABCB1* with neurotoxicity in response to taxane-based chemotherapy from lung cancer patients [28]. To the best of our knowledge no systematic studies have been carried out on BC patients to examine the severe chemotherapy induced toxicity reactions and their association with polymorphisms in drug transporter genes from Indian settings. Such ethnic specific genetic susceptibility information and its association with variety of chemotherapy drug induced toxicity can help in clinically important approach for treatment planning for the BC patients.

In conclusion, the findings obtained from this study depicted the significant protective association of 3435 C>T polymorphism of *ABCB1* with both heterozygous and homozygous variant genotype of *ABCB1* with severe chemotherapy induced non-hematological toxicity in BC patients treated with Adiramycin drug. The 3435 C>T polymorphisms of *ABCB1* also showed negative association with peripheral neuropathy in response to paclitaxel based chemotherapy in BC patients. This study is first of its own kind to understand the relationship between drug transporter gene polymorphism and Adriamycin or pacloitaxel based chemotherapy induced chemotherapy in breast cancer patients.

## Author Contribution Statement

Concept: RAG, SJB Design: RAG; KDD, AKG, Experimental Studies: KDD Clinical studies: RAG, AKG, Data analysis: KDD, RAG, Statistical analysis: KDD, Manuscript preparation: RAG, SJB, KDD, All authors read and approved the final manuscript.

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*Approval*

The study protocol was approved by protocol committee of Krishna Vishwa Vidyapeeth (Deemed to be University)

*Declaration of Conflict of interest*

The authors declare that they have no competing financial or any other conflict of interests that could have appeared to influence the work reported in this paper.

*Ethics Committee Approval*

The study protocol was approved by Institutional Ethics Committee of Krishna Vishwa Vidyapeeth 'Deemed to be University', Karad.

*Abbreviations*

BC: Breast Cancer
BMI: Body Mass Index
*ABCB1*:
PCR-RFLP: Polymerase Chain Reaction-Restriction Fragment Length Polymorphism
DNA: Deoxyribose Nucleic Acid
EDTA:
CINV: Chemotherapy Induced Nausea and Vomiting
ECOG: Estern Cooperative Oncology Group
NCI-CTC: National Cancer Institute-Common Toxicity Criteria
OR: Odds Ratio
CI: Confidence Interval
ER: Estrogen Receptor
PR: Progesterone receptor
Her2: Humen Epidermal Growth Factor Receptor

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