RESEARCH ARTICLE

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CYP2D6 and *CYP2E1* Gene Polymorphisms and Their Influence on Chemotherapy Treatment Outcome and Toxicity in Breast Cancer Patients

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Abstract

Background: The majority of breast cancer cases are treated with invasive chemotherapy, which typically involves combinations of drugs as part of the standard therapeutic regimen. However, responses to chemotherapeutic agents and treatment outcomes can vary significantly among patients, and the occurrence of acute toxicity remains unpredictable. Phase I drug detoxification genes, such as those encoding cytochrome P450 enzymes, play a crucial role in the metabolism of chemotherapeutic drugs in cancer patients. Therefore, this study aimed to investigate polymorphisms in the *CYP2D6* and *CYP2E1* genes and their potential association with adverse reactions to doxorubicin and paclitaxel-based chemotherapy in breast cancer patients. **Materials & Methods:** Genotyping of *CYP2D6**3, *CYP2D6**4, *CYP2D6**10, *CYP2D6**17, *CYP2E1**5B, *CYP2E1**6, *CYP2E1**7B genes was performed among 200 breast cancer patients undergoing chemotherapy, using the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method. The association between gene polymorphisms and chemotherapy-induced toxicity was assessed using odds ratios (ORs) with 95% confidence intervals and corresponding p-values, where $p \leq 0.05$ was considered statistically significant. **Results:** Following the analysis of *CYP2D6* and *CYP2E1* gene polymorphisms, we observed that *CYP2D6**4 (rs3892097, G>A) (OR = 4.71; 95% CI: 1.93–11.46; p = 0.0006), *CYP2D6**10 (rs1065852, C>T) (OR = 3.43; 95% CI: 1.43–8.21; p = 0.005), and *CYP2E1**6 (rs6413432, T>A) (OR = 4.00; 95% CI: 1.66–9.61; p = 0.001) showed a positive association with severe peripheral neuropathy induced by paclitaxel-based chemotherapy in breast cancer patients. Additionally, *CYP2E1**6 (rs6413432, T>A) (OR = 4.04; 95% CI: 1.72–9.50; p = 0.001) was significantly associated with paclitaxel-induced body ache in a subset of breast cancer patients. **Conclusion:** The findings from this study conclude that polymorphisms in the *CYP2D6* and *CYP2E1* genes are associated with peripheral neuropathy, a non-hematological toxicity reaction, in breast cancer patients receiving paclitaxel-based chemotherapy.

Keywords: Breast Cancer- *CYP2D6*- *CYP2E1*- Chemotherapy- Acute toxicity

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Introduction

Breast cancer (BC) is the most common type of invasive cancer among women, accounting for approximately 12.5% of all newly diagnosed cancer cases worldwide. It is also the second leading cause of cancer-related mortality in women. Nearly 60% of breast cancer deaths occur in economically developing regions of South America and Asia, including China, Pakistan, and India. BC is a heterogeneous and multifactorial disease characterized by diverse cellular origins and multiple molecular subtypes, with genetic factors increasingly recognized for their role in disease development [1–4]. The commonly adopted therapeutic strategy for managing breast cancer (BC) involves a combination of surgery, radiotherapy, chemotherapy, and targeted therapy. Chemotherapy is an aggressive modality used in conjunction with surgery or radiotherapy to improve treatment outcomes. Most breast cancers are managed with systemic adjuvant and neoadjuvant chemotherapy, wherein combinations of agents such as anthracyclines (doxorubicin, epirubicin), platinum compounds (cisplatin, carboplatin), and taxanes (paclitaxel, docetaxel) constitute the foundation of standard therapeutic regimens [5–7]. These chemotherapeutic drugs are primarily detoxified in the liver, where cytochrome P450 enzymes metabolize them into less toxic forms, while the kidneys aid in filtering the resulting drug metabolites. However, this detoxification process can occasionally generate reactive byproducts, contributing to chemotherapy-induced

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toxicity reactions, which may manifest as adverse effects on various organs and physiological systems. In breast cancer patients, these acute toxicity reactions are broadly categorized into hematological toxicities, such as anemia, neutropenia, febrile neutropenia, and thrombocytopenia and non-hematological adverse events including mucositis, chemotherapy-induced nausea and vomiting, fatigue, body ache, and peripheral neuropathy [8–10]. However, treatment responses and outcomes cannot be generalized across all patients, as the incidence and severity of acute toxicity are highly variable and often unpredictable. Acute hematological toxicities have been reported in approximately 40–80% of BC patients receiving both neoadjuvant and adjuvant chemotherapy [11]. Overall, non-hematological adverse drug reactions associated with both chemotherapy regimens have been observed in more than 80% of patients [12–13].

The cytochrome P450 enzyme system constitutes a critical component of the phase I detoxification pathway, wherein multiple CYP gene isoforms including *CYP1A1, CYP1B1, CYP2B6, CYP2C9, CYP2C19, CYP2D6*, and *CYP2E1* are involved in the metabolism of various xenobiotics and therapeutic agents. The *CYP450* family is highly polymorphic, and functional genetic variations in these enzymes have been associated with cancer susceptibility [14–15]. Among these, *CYP2D6* and *CYP2E1* encoded by the *CYP2D6* and *CYP2E1* genes respectively, are key phase I enzymes essential for the biotransformation of xenobiotic compounds within the human body. Number of studies have explored the functional association between polymorphisms in the *CYP2D6* and *CYP2E1* genes and altered susceptibility to various cancers, including esophageal and colorectal cancer [16–17], and more recently, breast [18] and bladder cancer [19]. Although direct evidence linking *CYP2D6* and *CYP2E1* polymorphisms to breast cancer risk remains limited, their role in the metabolism of carcinogens and endogenous hormones suggests a potential influence on patient responses to chemotherapeutic agents. Thus, the selection of these polymorphisms for their potential association with doxorubicin and paclitaxel metabolism is justified in the context of BC risk prediction and toxicity outcomes. Previous studies have also reported an association between *CYP2D6* polymorphisms and breast cancer risk in the South Indian population [20]. *CYP2E1* is a key enzyme involved in the metabolism of various dietary procarcinogens, including nitrosamines, heterocyclic amines, and polycyclic aromatic hydrocarbons. Polymorphisms in this gene may lead to reduced enzymatic activity, impairing carcinogen detoxification and thereby influencing individual susceptibility to increased cancer risk. The impact of genetic polymorphisms in *CYP2D6* and *CYP2E1* genes on BC outcomes in response to doxorubicin- and paclitaxel-based chemotherapy remains uncertain in clinical settings. Therefore, this study aimed to identify and evaluate the association of *CYP2D6**3 (rs35742686), *CYP2D6**4 (rs3892097), *CYP2D6**10 (rs1065852), *CYP2D6**17 (rs28371706), *CYP2E1**5B (rs2031920), *CYP2E1**6 (rs6413432), and *CYP2E1**7B (rs6413420) polymorphisms with chemotherapy-induced toxicity reactions in BC patients receiving treatment with doxorubicin and paclitaxel.

Materials and Methods

Patient enrollment and Clinical Information

Two hundred (200) clinically confirmed and histologically diagnosed BC patients visiting the Medical Oncology Outpatient Department (OPD) for treatment at the Department of Oncology, Krishna Hospital & Medical Research Center, Krishna Vishwa Vidyapeeth (Deemed to be University), Karad, were enrolled based on predefined inclusion and exclusion criteria. The sample size was calculated by the formula n= [(p1xq1) + (p2 x p2)] X ($Z_{1-\alpha/2}$) +$Z_{1-\beta)2}$/ (p1-p2)^2 with 95%confidence and 95% power; Where p1- presence of allele1, q1- absence of allele1, p2- presence of allele 2, q2- absence of allele 2, α- probability of detecting false results and β- power. The Inclusion criteria are; patients with age range of 18 to 85 years age diagnosed with BC, histopathologically confirmed, no metastasis at diagnosis, clinically localised or locally advanced tumors according to standard staging system, patients diagnosed with BC who were planned to receive adjuvant chemotherapy postoperatively with standard doxorubicin and cyclophosphamide chemotherapy followed by paclitaxel chemotherapy, and locally advanced BC patients receiving neoadjuvant chemotherapy for downstaging. The exclusion criteria are; no pathological diagnosis, male BC Patients, relapsed disease or metastasis, associated severe co-morbidities, auto immune disease, no or incomplete treatment taken, incomplete follow-up, missing or incomplete data, patients with abnormal renal or liver function tests at the time of enrollment and patients with performance score of Eastern Cooperative Oncology Group (ECOG) ≥2. The study protocol was approved by Institutional Ethics Committee of Krishna Institute of Medical Sciences for the utilization of human subjects in the research (KIMSDU/IEC/01/2018 dated 2nd February 2018)

Chemotherapy Treatment Regimen follow up and Toxicity Assessment

Once the patient was enrolled in the study after fulfilling inclusion and exclusion criteria,written informed consent was taken and chemotherapy was planned as per the stage of the patient. Patients received 4 cycles of combination chemotherapy with doxorubicin and cyclophosphamide , 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 post-chemotherapy for assessing chemotherapy related toxicities. 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. Patient were 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 [21]. The patients were routinely tested for blood and urine along with

complete blood count, renal function and liver function test before each chemotherapy cycle to monitor health and to check chemotherapy induced side effects. The hematological toxicities including anemia, neutropenia, thrombocytopenia and non-hematological toxicities such as mucositis, chemotherapy induced nausea/vomiting (CINV), fatigue, body ache, 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 *CYP2D6* and *CYP2E1* 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.

Blood Sample Collection and Genomic DNA Extraction and Purification

Five milliliter (mL) of whole blood from 200 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 (HiMedia Laboratories) following the manufacturer's instructions. This pure genomic DNA was used for genotyping assays by polymerase chain reaction (PCR) and Restriction fragment Length Polymorphism (RFLP).

Genotyping assays of CYP2D6 and CYP2E genes

The genotyping of *CYP2D6**3, *CYP2D6**4, *CYP2D6**10, *CYP2D6**17, *CYP2E1**5B, *CYP2E1**6, *CYP2E1**7B genes was performed by PCR-RFLP. The PCR amplification were 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 DNA polymerase (GeNei, Merck Bioscience) and 100 nanogram (ng) of purified genomic DNA. The primer sequence used to amplify the *CYP2D6* and *CYP2E1* genes and the PCR conditions are shown in Table 1.

Restriction Fragment Length Polymorphism

After performing PCR programme for each reaction, the PCR products were analysed by agarose gel electrophoresis in Tris-Acetate-EDTA (TAE) buffer. After confirmation of DNA amplification, each PCR product was digested with an appropriate restriction enzyme with specific conditions for genotyping. Ten micro litters of the PCR products digested at 37°C overnight with specific restriction enzymes in 20 μL reaction mixtures containing buffer supplied with each restriction enzyme (Table 1). After the overnight incubation, digestion products were separated on a 2-3% low EEO agarose (GeNei) gel at 100 V for 30 min stained with ethidium bromide and photographed with gel documentation system (BioRad). The results obtained by PCR-RFLP analysis were further validated by direct DNA sequencing of amplified PCR products of some randomly selected representative samples which also confirmed the polymorphism in selected genes (Figure 1).

Statistical Analysis

A univariate logistic regression model was employed to assess the effect of genetic polymorphisms in the *CYP2D6* and *CYP2E1* genes on the incidence of chemotherapy-induced toxicity (Grade 0–1 vs. Grade 2–4). Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were calculated using unconditional multiple logistic regression. Clinical severity of post-chemotherapy adverse effects was classified into hematological and non-hematological toxicity reactions, with Grade >1 considered clinically significant. Multivariate analysis was conducted to adjust for demographic and clinicopathological variables influencing chemotherapy toxicity. Associations between each polymorphism and the severity of toxicities were further evaluated using chi-square tests. p-values < 0.05 were regarded as statistically significant. Genotype frequency data were assessed for Hardy–Weinberg equilibrium using SPSS version 11.0 software.

Results

A total of 200 clinically confirmed BC patients were enrolled in this study, with ages ranging from 18 to 85 years and a mean age of 50.24 years. Among them, 157 patients (78.5%) were above 40 years of age. Based on body mass index (BMI), 122 women (61%) had a BMI ≤ 25, while 78 women had a BMI > 25. Regarding menopausal status, 70 patients (35%) were classified as premenopausal and 130 patients (65%) as postmenopausal for the evaluation of treatment outcomes and other clinical parameters. Of the cohort, 155 women received adjuvant chemotherapy, 31 patients underwent neoadjuvant chemotherapy, and 14 patients were administered palliative chemotherapy. Hormone receptor status, assessed via immunohistochemistry, revealed 83 patients to be ER/PR positive, 109 patients to be ER/PR negative, and 85 patients exhibited triple-negative breast cancer. Tumor size exceeded 2 cm in 95 patients (range: 2–10 cm), while 105 patients (52.5%) presented with tumors ≤ 2 cm. Clinically, 98 patients were staged at TNM stages III and IV, and histopathologically, 110 patients were classified at TNM stages III and IV (Table 2).

Genotype distribution of CYP2D6 and CYP2E1 gene polymorphisms and their association with doxorubicin based chemotherapy toxicity in BC patients

The polymorphism *CYP2D6**3, *CYP2D6**4, *CYP2D6**10, *CYP2D6**17, *CYP2E1**5B, *CYP2E1**6, and *CYP2E1**7B genes were investigated in this study. Out of 200 BC patients, 104 patients were first administered with doxorubicin followed by paclitaxel chemotherapy whereas 96 patients were first treated with paclitaxel and then doxorubicin. The chemotherapy induced acute toxicity reactions were grouped into hematological and non-hematological toxicities and graded into grade ≤1 or >1 toxicities. Chemotherapy-induced acute toxicity reactions were categorized into hematological and non-hematological toxicities and graded as ≤1 (mild) or >1 (severe). Hematological toxicities, including anemia, neutropenia, febrile neutropenia, and thrombocytopenia,

Table 1. The List of Candidate *CYP2D6* and *CYP2E1* Genes Selected in the Present Study with Details of PCR and RFLP Procedures Including Details of Primers and Their Sequences, Restriction Enzymes and Expected base Pairs of Expected PCR Products

Gene/ Genotype	rs number	Nucleotide change	Primer Sequence (Forward/Reverse)	PCR Conditions	PCR product size	Enzyme / Digestion conditions	Dominant Wild type (bp)	Heterozygous (bp)	Recessive Mutant (bp)
*CYP2D6**3 2549delA	rs35742686	(A>- (del A)	FP: 5'-ATG AGC TGC TAA CTG AGC CC -3' RP: 5'- CCG AGA GCA TAC TCG GGA C -3'	95°C for 5 min , 30 cycles of 95°C- 30 sec, 54°C- 45 sec, 72°C- 60 sec , final extension 72°C for 5 min	270 bp	1 Unit of MspI Incubation at 37°C for 16h	188 bp, 82 bp	188 bp, 168 bp 20 bp	168 bp, 20 bp
*CYP2D6**4 1846G>A	rs3892097	(G>A)	FP: 5'-GCT TCG CCA ACC ACT CCG-3' RP: 5'-AAA TCC TGC TCT TCC GAG GC-3'	95°C for 5 min, 30 cycles of 95°C- 20 sec, 57°C- 20 sec, 72°C- 20 sec ,final extension 72°C for 5 min	334 bp	1 Unit of BstO1 Incubation at 37°C for 1h	230 bp, 105 bp	334 bp, 230 bp 105 bp	334 bp
*CYP2D6**10 100C>T	rs1065852	(C>T)	FP: 5'- GTG CTG AGA GTG TCC TGC C -3' RP: 5'- CAC CCA CCA TCC ATG TTT GC -3'	95°C for 5 min, 30 cycles of 95°C- 60 sec, 53°C- 60 sec, 72°C- 60 sec, final extension 72°C for 5 min	344 bp	1 Unit of HphI Incubation at 37°C for 16h	282 bp, 62 bp	282 bp, 182 bp, 100bp, 62bp	182 bp, 100 bp 62 bp
*CYP2D6**17 1023C>T	rs28371706	(C>T)	FP: 5'- CGG TGG TCG TGC CTC AAT G -3' RP: 5'- CCC GGG TCC CAC GGA AAT CT -3'	95°C for 5 min, 30 cycles of 95°C- 30 sec, 55°C- 45 sec, 72°C- 60 sec, final extension 72°C for 5 min	167 bp	1 Unit of HphI Incubation at 37°C for 1h	167 bp	167 bp, 88 bp 55bp	88 bp, 55 bp
*CYP2E1**5B 1293G>C	rs2031920	(G>C)	FP: 5'-ACC CCA ATG GGT GTC TGT C-3' RP: 5'-TCA TTC TGT CTT CTA ACT GGC AAT-3'	95°C for 5 min , 30 cycles of 95°C- 30 sec, 54°C- 45 sec, 72°C- 30 sec , final extension 72°C for 5 min	576 bp	1 Unit of PstI Incubation at 37°C for 1h	294 bp, 284 bp	576 bp, 294 bp 282 bp	576 bp
*CYP2E1**6 7632T>A	rs6413432	(T>A)	FP: 5'-AGG CTC GTC AGT TCC TGA AA -3' RP: 5'-AAG GCA GGA GGA TGA CTT GA -3'	95°C for 5 min, 30 cycles of 95°C- 20 sec, 62°C- 25 sec, 72°C- 20 sec, final extension 72°C for 5 min	685 bp	1 Unit of DraI Incubation at 37°C for 1h	376 bp, 309 bp	685 bp, 376 bp 309 bp	685 bp
*CYP2E1**7B 71G>T	rs6413420	(G>T)	FP: 5'-CTG GAG TTC CCC GTT GTC TA-3' RP: 5'-GGG TGA AGG ACT TGG GAA TA -3'	95°C for 5 min, 30 cycles of 95°C- 30 sec, 54°C- 45 sec, 72°C- 30 sec, final extension 72°C for 5 min	547 bp	1 Unit of DdeI Incubation at 37°C for 1h	301 bp, 246 bp	547 bp, 301 bp 246 bp	547 bp

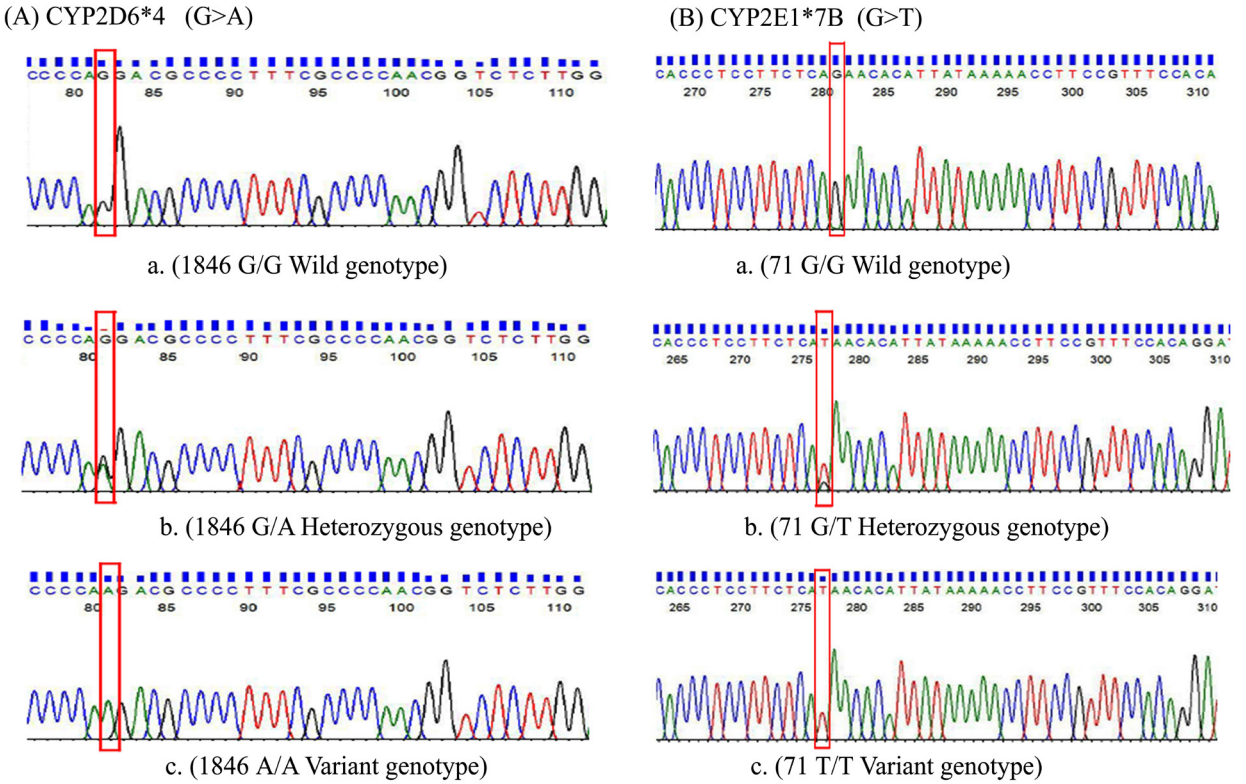

Figure 1. Representative Chromatogram of Corresponding DNA Sequence Showing Nucleotide Change Position. (A) *CYP2D6**4 is represented by G>A substitution at nucleotide 1846 of exon-4. (a) A sample with Normal 'G' allele (b) Sample with heterozygous G/A genotype and (c) Sample with homozygous variant A/A genotype for *CYP2D6**4 (rs3892097) polymorphism (B) *CYP2E1**7B polymorphism with G>T substitution of SNP rs6413420 (a) A sample with normal 'G/G' genotype. (b) A sample with major 'G/T' genotype in 71 G>T and (c) sample with homozygous variant (T/T) genotype of *CYP2E1**7B (rs6413420) polymorphism.

were evaluated through blood testing. Non-hematological toxicities such as mucositis, CINV, fatigue, body ache, and peripheral neuropathy were documented through physical examination. Among 104 patients who received treatment with doxorubicin followed by paclitaxel, 23 patients exhibited severe anemia (Grade >1), 25 developed severe neutropenia, 24 experienced febrile neutropenia, and 7 presented with thrombocytopenia. Severe non-hematological toxicities (Grade >1) were recorded as follows: mucositis in 16 patients, CINV in 34 patients, fatigue in 37 patients, body ache in 15 patients, and peripheral neuropathy in 5 patients following doxorubicin administration. The univariate logistic regression analysis was used to find out an association of *CYP2D6**3 (rs35742686, A>T), *CYP2D6**4 (rs3892097, G>A), *CYP2D6**10 (rs1065852, C>T), *CYP2D6**17(rs28371706, C>T), *CYP2E1**5B (rs2031920, G>C), *CYP2E1**6 (rs6413432,T>A), and *CYP2E1**7B (rs6413420, G>T) single nucleotide polymorphisms (SNPs) with standard doxorubicin based chemotherapy induced acute toxicity reactions in BC patients. In our investigation of the correlation between genetic polymorphisms in the *CYP2D6* and *CYP2E1* genes and severe hematological toxicity reactions in patients undergoing doxorubicin chemotherapy, the analysis revealed significant findings. The *CYP2D6**10 polymorphism exhibited a negative association (OR = 0.32; 95% CI: 0.10–0.94; p = 0.039), suggesting a protective effect against febrile neutropenia in breast cancer patients. Similarly, *CYP2E1**5B showed a significant negative association (OR = 0.05; 95% CI: 0.03–0.90; p = 0.04) with neutropenia in the same patient cohort (Table 3). Similarly, when we investigated the association between genetic polymorphisms in the *CYP2D6* and *CYP2E1* genes and non-hematological toxicity reactions including mucositis CINV, fatigue, body ache, and peripheral neuropathy in patients treated with doxorubicin, the analysis revealed no correlation for *CYP2D6**3, *CYP2D6**4, *CYP2D6**10, *CYP2E1**5B, *CYP2E1**6, and *CYP2E1**7B polymorphisms. However, a significant association was observed between the *CYP2D6**17 polymorphism and CINV in breast cancer patients receiving doxorubicin-based chemotherapy (OR = 2.58; 95% CI: 1.11–6.60; p = 0.026) (Table 4).

Correlation of genetic variants of CYP2D6 and CYP2E1 gene polymorphisms and paclitaxel based chemotherapy toxicity in BC patients

When the genotype distribution of *CYP2D6**3, *CYP2D6**4, *CYP2D6**10, *CYP2D6**17, *CYP2E1**5B, *CYP2E1**6, and *CYP2E1**7B was examined in patients treated with paclitaxel-based chemotherapy, the analysis revealed a significant association between the *CYP2E1**7B (rs6413420, G>T) single nucleotide polymorphism (SNP) and hematological toxicity, specifically anemia, in breast

Table 2. Details of Demographic and Clinico-Pathological Characteristics of Breast Cancer Patients Enrolled in the Study

Variables	Number	Percentage (%)
Total Number of patients	200	
Age (Mean ± SD) years	50.24 ±10.93	(Range:18-85) Median:48
≤ 50	118	59
>50	82	41
BMI Kg/m^2		
<25	122	61
25-30	62	31
>30	16	8
Tobacco smoking Status		
Tobacco users	109	54.5
Tobacco no users	91	45.5
Family history of Cancer		
Yes	50	25
No	150	75
Tumor localization		
Left breast	102	51
Right breast	98	49
Tumor size in cm		
≤ 2	105	52.5
> 2	95	47.5
Histological Grade		
I, II	107	53.5
III, IV	93	46.5
Clinical TNM Stage		
I	4	2
II	98	49
III	80	40
IV	18	9
Histopathological TNM Stage		
I	2	1
II	88	44
III	90	45
IV	20	10
Hormone Receptor Status		
ER/ PR+ve	83	41.5
ER/ PR-ve	109	54.5
ER/PR/Her2+ve	6	3
ER/PR/Her2-ve	85	42.5
ER/ PR+ve Her2-ve	78	39
ER/ PR-ve Her2+ve	24	12
Chemotherapy		
Adjuvant chemotherapy	155	77.5
Neo-Adjuvant chemotherapy	31	15.5
Palliative chemotherapy	14	7
Radiotherapy		
Adjuvant RT	81	40.5
No Adjuvant RT	119	59.5

cancer patients (OR = 342.00; 95% CI: 33.04–354.60; p < 0.0001). In contrast, no significant associations were observed between the other genotypes and anemia or other hematological toxicities (Supplementary Table 1). Similarly, in our investigation of *CYP2D6* gene polymorphisms in relation to non-hematological acute toxicities induced by paclitaxel-based chemotherapy, we observed that the variant genotypes *CYP2D6**4 (rs3892097, G>A) (OR = 4.71; 95% CI: 1.93–11.46; p = 0.0006) and *CYP2D6**10 (rs1065852, C>T) (OR = 3.43; 95% CI: 1.43–8.21; p = 0.005) exhibited significant associations with peripheral neuropathy, a non-hematological toxicity reaction triggered by paclitaxel chemotherapy. Similarly, analysis of *CYP2E1* polymorphism revealed a positive association between *CYP2E1**6 (rs6413432, T>A) and paclitaxel-induced peripheral neuropathy in BC patients (OR = 4.00; 95% CI: 1.66–9.61; p = 0.001). Likewise, our findings indicated a significant association of the same polymorphism with paclitaxel-induced body ache in BC patients (OR = 4.04; 95% CI: 1.72–9.50; p = 0.001) (Supplementary Table 2).

Association of CYP2D6 and CYP2E1 polymorphisms with demographic and clinic-pathological factors of BC patients

Upon analyzing the correlation between genetic polymorphisms in the *CYP2D6* and *CYP2E1* genes and the demographic and clinicopathological characteristics of BC patients, no significant association was observed between any of the *CYP2D6* or *CYP2E1* genotypes and the evaluated demographic or clinicopathological features. The results pertaining to the polymorphisms *CYP2D6**3 (rs35742686, A>–), *CYP2D6**4 (rs3892097, G>A), *CYP2D6**10 (rs1065852, C>T), *CYP2D6**17 (rs28371706, C>T), *CYP2E1**5B (rs2031920, G>C), *CYP2E1**6 (rs6413432, T>A), and *CYP2E1**7B (rs6413420, G>T), and their association with the demographic and clinicopathological characteristics of BC patients are presented in Supplementary Table 3. When demographic factors, including age and body mass index (BMI), were considered for the BC patients enrolled in this study, the analysis revealed no association between *CYP2D6* or *CYP2E1* variant genotypes and patients' age or BMI. The present study also found no association between *CYP2D6* SNPs (rs35742686, rs3892097, rs1065852, rs28371706) or *CYP2E1* SNPs (rs2031920, rs6413432, rs6413420) and histopathological TNM stage > II. However, clinical TNM stage > II showed a significant association with the *CYP2E1**7B (rs6413420, G>T) polymorphism (OR = 5.05; 95% CI: 1.06–24.02; p = 0.041). The analysis of genotype distributions for *CYP2D6* and *CYP2E1* polymorphisms revealed no significant association with hormonal receptor status (ER/PR or *HER2*) in BC patients. However, our data indicated a significant correlation between the *CYP2E1**7B (rs6413420, G>T) SNP and select demographic and clinicopathological characteristics of BC patients examined in this study. Furthermore, in our evaluation of the relationship between demographic and clinicopathological factors and chemotherapy-induced toxicity reactions, we observed that a higher BMI was negatively correlated with non-hematological toxicities,

Table 3. Univariate Analysis of Candidate SNPs of *CYP2D6, CYP2E1* Gene and Risk of Doxorubicin Chemotherapy Induced Severe Toxicity of Hematological Reactions in Breast Cancer Patients

		Anemia				Neutropenia			
Gene Name SNP	Genotype	Grade≤1 (n=81)	Grade >1 (n=23)	OR (95% CI)	p value	Grade ≤1 (n=79)	Grade >1 (n=25)	OR (95% CI)	p value
*CYP2D6**3	A/A	49	14	1 (Reference)		48	15	1 (Reference)	
rs35742686	A/- + -/-	32	9	0.98 (0.38-2.54)	0.974	31	10	1.03 (0.41-2.58)	0.946
*CYP2D6**4	G/G	51	13	1 (Reference)		51	13	1 (Reference)	
rs3892097	G/A+A/A	30	10	1.80 (0.72-4.51)	0.203	28	12	1.68 (0.67-4.17)	0.263
*CYP2D6**10	C/C	47	16	1 (Reference)		46	17	1 (Reference)	
rs1065852	C/T+T/T	34	7	0.60 (0.22-1.63)	0.32	33	8	0.65 (0.25-1.69)	0.385
*CYP2D6**17	C/C	50	12	1 (Reference)		46	16	1 (Reference)	
rs28371706	C/T+T/T	31	11	1.47 (0.58-3.75)	0.411	33	9	0.78 (0.30-1.98)	0.608
*CYP2E1**5B	G/G	79	23	1 (Reference)		77	25	1 (Reference)	
rs2031920	G/C+C/C	2	0	0.67 (0.03-14.59)	0.803	28	0	0.05 (0.03-0.90)	0.042*
*CYP2E1**6	T/T	51	12	1 (Reference)		48	15	1 (Reference)	
rs6413432	T/A+A/A	30	11	1.55 (0.61-3.96)	0.352	31	10	1.03 (0.41-2.58)	0.946
*CYP2E1**7B	G/G	74	23	1 (Reference)		72	25	1 (Reference)	
rs6413420	G/T+T/T	7	0	0.21 (0.01-3.84)	0.293	7	0	0.18 (0.01-3.43)	0.26
		Febrile Neutropenia				Thrombocytopenia			
		Grade ≤1 (n=80)	Grade >1 (n=24)			Grade ≤1 (n=97)	Grade >1 (n=7)		
*CYP2D6**3	A/A	45	18	1 (Reference)		58	5	1 (reference)	
rs35742686	A/- + -/-	35	6	0.42 (0.15-1.19)	0.104	39	2	0.59 (0.10-3.22)	0.546
*CYP2D6**4	G/G	53	10	1 (Reference)		61	3	1 (reference)	
rs3892097	G/A+A/A	27	14	1.85 (0.73-4.67)	0.188	36	4	2.25 (0.47-10.67)	0.303
*CYP2D6**10	C/C	44	19	1 (Reference)		59	4	1 (reference)	
rs1065852	C/T+T/T	36	5	0.32 (0.10-0.94)	0.039*	38	3	1.16 (0.24-5.49)	0.847
*CYP2D6**17	C/C	48	14	1 (Reference)		57	5	1 (reference)	
rs28371706	C/T+T/T	32	10	1.07 (0.42-2.70)	0.884	40	2	0.57 (0.10-3.08)	0.514
*CYP2E1**5B	G/G	78	24	1 (Reference)		95	7	1 (reference)	
rs2031920	G/C+C/C	2	0	0.64 (0.02-13.80)	0.776	2	0	2.54 (0.11-58.02)	0.557
*CYP2E1**6	T/T	49	14	1 (Reference)		60	3	1 (reference)	
rs6413432	T/A+A/A	31	10	1.12 (0.44-2.85)	0.797	37	4	2.16 (0.45-10.20)	0.33
*CYP2E1**7B	G/G	73	24	1 (Reference)		90	7	1 (reference)	
rs6413420	G/T+T/T	7	0	0.20 (0.01-3.63)	0.276	7	0	0.80 (0.04-15.49)	0.885

SNP, Single nucleotide polymorphism; OR, Odds ratio; CI, Confidence interval; * indicates significance $p< 0.05$; p value determined based on χ^2.

Table 4. Univariate Analysis of Candidate SNPs of *CYP2D6, CYP2E1* Genes and Risk of Doxorubicin Chemotherapy Induced Severe Toxicity of Non- Hematological Reactionsin Breast Cancer Patients.

		Anemia				Neutropenia			
Gene Name SNP	Genotype	Grade ≤1 (n=88)	Grade >1 (n=16)	OR (95% CI)	p value	Grade ≤1 (n=70)	Grade >1 (n=34)	OR (95% CI)	p value
*CYP2D6*3*	A/A	53	10	1 (Reference)		41	22	1 (Reference)	
rs35742686	A/- + -/-	35	6	0.90 (0.30-2.72)	0.864	29	12	0.77 (0.32-1.80)	0.548
*CYP2D6*4*	G/G	56	8	1 (Reference)		43	21	1 (Reference)	
rs3892097	G/A+A/A	32	8	1.75 (0.59-5.11)	0.306	27	13	0.98 (0.42-2.28)	0.973
*CYP2D6*10*	C/C	56	7	1 (Reference)		45	18	1 (Reference)	
rs1065852	C/T+T/T	32	9	2.25 (0.76-6.61)	0.14	25	16	1.60 (0.69-3.67)	0.268
*CYP2D6*17*	C/C	53	9	1 (Reference)		47	15	1 (Reference)	
rs28371706	C/T+T/T	35	7	1.17 (0.40-3.45)	0.765	23	19	2.58 (1.11-6.00)	0.026*
*CYP2E1*5B*	G/G	86	16	1 (Reference)		69	33	1 (Reference)	
rs2031920	G/C+C/C	2	0	1.04 (0.04-22.85)	0.976	1	1	2.09 (0.12-34.43)	0.606
*CYP2E1*6*	T/T	52	11	1 (Reference)		41	22	1 (Reference)	
rs6413432	T/A+A/A	36	5	0.65 (0.21-2.05)	0.469	29	12	0.77 (0.32-1.80)	0.548
*CYP2E1*7B*	G/G	81	16	1 (Reference)		63	34	1 (Reference)	
rs6413420	G/T+T/T	7	0	0.32 (0.01-6.05)	0.454	7	0	0.12 (0.06-2.21)	0.155
		Fatigue				Bodyache			
		Grade ≤1 (n=67)	Grade >1 (n=37)			Grade ≤1 (n=89)	Grade >1 (n=15)		
*CYP2D6*3*	A/A	43	20	1 (Reference)		53	10	1 (Reference)	
rs35742686	A/- + -/-	24	17	1.52 (0.67-3.44)	0.312	36	5	0.73 (0.23-2.33)	0.602
*CYP2D6*4*	G/G	42	22	1 (Reference)		57	7	1 (Reference)	
rs3892097	G/A+A/A	25	15	1.14 (0.50-2.60)	0.746	32	8	2.03 (0.67-6.13)	0.206
*CYP2D6*10*	C/C	44	19	1 (Reference)		54	9	1 (Reference)	
rs1065852	C/T+T/T	23	18	1.81 (0.79-4.10)	0.154	35	6	1.02 (0.33-3.14)	0.96
*CYP2D6*17*	C/C	37	25	1 (Reference)		54	8	1 (Reference)	
rs28371706	C/T+T/T	30	12	0.59 (0.25-1.37)	0.221	35	7	1.35 (0.44-4.05)	0.592
*CYP2E1*5B*	G/G	65	37	1 (Reference)		87	15	1 (Reference)	
rs2031920	G/C+C/C	2	0	0.34 (0.01-7.47)	0.509	2	0	1.12 (0.05-24.66)	0.938
*CYP2E1*6*	T/T	40	23	1 (Reference)		55	8	1 (Reference)	
rs6413432	T/A+A/A	27	14	0.90 (0.39-2.05)	0.805)	34	7	1.41 (0.47-4.25)	0.536
*CYP2E1*7B*	G/G	62	35	1 (Reference)		82	15	1 (Reference)	
rs6413420	G/T+T/T	5	2	0.70 (0.13-3.84)	0.689	7	0	0.35 (0.01-6.53)	0.485

SNP, Single nucleotide polymorphism; OR, Odds ratio; CI, Confidence interval; * indicates significance $p< 0.05$; p value determined based on χ^2.

specifically mucositis (p = 0.01) and body ache (p = 0.003), following doxorubicin treatment. Moreover, patients with clinical and histopathological TNM staging beyond stage II exhibited a significant association with chemotherapy-induced nausea and vomiting in response to doxorubicin, with p-values of 0.046 and 0.035, respectively. However, our study did not reveal any significant correlations between demographic or clinicopathological factors and outcomes associated with paclitaxel-based chemotherapy

Discussion

Chemotherapeutic drugs used in cancer treatment are recognized for their specific targeted mechanisms of action; however, a substantial gap persists in understanding the pharmacological mechanisms of many chemotherapy drugs. Consequently, it is essential to investigate the genetic diversity of individuals undergoing chemotherapy, as it significantly influences their susceptibility to both therapeutic efficacy and adverse drug reactions. Examining single nucleotide polymorphisms in genes responsible for drug detoxification can provide valuable insights into their role in modulating chemotherapy responses. While numerous studies have explored genetic variations in drug metabolism-related genes and their associations with cancer susceptibility, limited data are available regarding their impact on chemotherapy treatment outcomes across various cancer types. Therefore, identifying key genetic polymorphisms in drug detoxification genes is essential for enhancing chemotherapeutic efficacy and minimizing toxicity in breast cancer patients. Several pharmacogenomic studies have demonstrated that patients respond differently to various chemotherapy drugs due to the diverse genetic susceptibility of each individual to treatment. The CYP genes are highly polymorphic in nature, encompassing multiple isozymes such as *CYP1A1, CYP1B1, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP2E1*, and *CYP17*, each of which exhibits functional polymorphisms. These genetic variations have notable clinical relevance, as they can alter drug efficacy and contribute to therapeutic failure and adverse toxicity effects [22–24]. Pharmacogenomic studies have demonstrated that polymorphisms in *CYP450* genes can significantly influence therapeutic efficacy and treatment outcomes associated with various chemotherapeutic agents [25–26]. The drug transporter *ABCB1* gene, with its C1236T and C3435T variants, has been extensively investigated for its diverse distribution among different ethnic groups. Previous research has established a link between genetic variations in the *ABCB1* gene and alterations in response to a broad spectrum of chemotherapeutic agents. Numerous studies have highlighted the impact of ABCB1 gene polymorphisms on chemotherapy-induced toxicities in breast cancer patients, as demonstrated by Wu et al. [27] and Chaturvedi et al. [28]. Previous reports have demonstrated that polymorphisms in the *CYP450* gene family are associated with therapeutic failure and severe chemotherapy-induced toxicity reactions [29–31]. Association studies have indicated a significant correlation between the *CYP2E1* T>A (rs6413432) polymorphism and outcomes of platinum-based chemotherapy in cervical cancer patients [32]. Conversely, other studies have reported no significant impact of *CYP2D6**1A, *CYP2E1**6, and *CYP2E1**7B polymorphisms on clinical responses to either platinum- or taxane-based chemotherapy in patients with non-small cell lung carcinoma [33–34]. Functional polymorphisms in *CYP1A1, CYP1B1, CYP2B6, CYP2C8,* and *CYP2C9* play a crucial role in clinical outcomes by influencing drug efficacy and potentially contributing to therapeutic inefficacy and adverse toxicity across various cancers [29–33], including breast cancer [35, 36]. Similarly, the polymorphism of *CYP2C19* and its association with hematological toxicities, including neutropenia, has been previously reported in response to chemotherapeutic drugs administered for ovarian [37], breast [38, 39], lung cancer [40], and non-small cell lung carcinoma [34]. In our prior study, we observed a significant association between the *CYP2C19**2 (681 G>A) polymorphism and hematological toxicities including anemia, neutropenia, febrile neutropenia, and thrombocytopenia in BC patients treated with doxorubicin. Furthermore, a significant association was noted between the *CYP2C19**2 polymorphism and non-hematological toxicities such as chemotherapy-induced nausea and vomiting, fatigue, and peripheral neuropathy in response to paclitaxel-based chemotherapy [41]. Unlikely, we observed a negative association between *CYP1A1, CYP1B1*, and *CYP2C9* polymorphisms and peripheral neuropathy in BC patients treated with paclitaxel-based chemotherapy [42]. The *ABCB1* and *CYP2D6* genes have been shown to regulate the metabolism and pharmacokinetics of doxorubicin [43]. Polymorphisms in *CYP2C9, CYP2C19*, and *CYP2D6* associated with poor metabolizer phenotypes demonstrated a significant correlation with decreased drug efficacy in breast cancer treatment [44]. This study examined the association of polymorphisms in drug detoxification genes (*CYP2D6* and *CYP2E1*) with hematological and non-hematological toxicities following doxorubicin- and paclitaxel-based chemotherapy in BC patients. Analysis of seven genetic variants including *CYP2D6**3 (rs35742686), *CYP2D6**4 (rs3892097), *CYP2D6**10 (rs1065852), *CYP2D6**17 (rs28371706), *CYP2E1**5B (rs2031920), *CYP2E1**6 (rs6413432), and *CYP2E1**7B (rs6413420) revealed a negative association of *CYP2E1**5B (rs2031920) with neutropenia and *CYP2D6**10 (rs1065852) with febrile neutropenia following doxorubicin-based chemotherapy. The *CYP2D6**17 (rs28371706) polymorphism was significantly associated with doxorubicin-induced CINV in BC patients. Additionally, the *CYP2D6**4 (rs3892097) variant genotype demonstrated a significant positive correlation with paclitaxel-induced peripheral neuropathy (OR = 4.71; 95% CI: 1.93–11.46; p < 0.0006). The findings of this study align with previous reports demonstrating a positive association between *CYP2E1* polymorphism and platinum-based chemotherapy outcomes in cervical cancer patients [27]. In BC patients treated with paclitaxel, the *CYP2E1**7B (rs6413420) polymorphism showed a significant association with anemia (OR = 342.00; 95% CI: 33.04–354.60; p < 0.0001). Paclitaxel-induced body ache showed a significant association with the

*CYP2E1**6 (rs6413432) polymorphism (OR = 4.00; 95% CI: 1.66–9.61; $p < 0.001$) in BC patients. In contrast, other studies reported no significant impact of *CYP2D6**1A, *CYP2E1**6, and *CYP2E1**7B polymorphisms on platinum- or taxane-based chemotherapy response in non-small cell lung carcinoma patients [31, 33–34]. Notably, the genotype distribution of *CYP2D6* and *CYP2E1* exhibited significant deviation from Hardy–Weinberg equilibrium in patients experiencing paclitaxel-induced hematological and non-hematological toxicities. To our knowledge, this is the first study from India investigating the role of metabolic *CYP450* gene polymorphisms in doxorubicin/paclitaxel-related chemotherapy toxicities in breast or other cancers.

Conclusion: In conclusion, the *CYP2D6* polymorphism demonstrated a positive association with paclitaxel-induced peripheral neuropathy, while the *CYP2E1**6 (rs6413432) polymorphism showed a significant correlation with body ache in BC patients. This is the first study of its kind to analyze the influence of doxorubicin-based chemotherapy on metabolic gene polymorphisms in BC patients. However, larger-scale studies are necessary to validate and strengthen the observed associations between genetic variants of *CYP2D6* and *CYP2E1* and chemotherapy outcomes in BC by increasing both the sample size and the number of SNPs included for genotyping.

Author Contribution Statement

Concept: RAG, AKG, SJB Design: KDD, RAG, Experimental Studies: RAG, KDD Clinical studies: RAG, AKG Data analysis: KDD, RAG, Statistical analysis: KDD Manuscript preparation: RAG, KDD, AKG, 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
CYP450: Cytochrome P450
PCR-RFLP: Polymerase Chain Reaction-Restriction Fragment Length Polymorphism
DNA: Deoxyribose Nucleic Acid
EDTA: Ethylenediamdie Tetra acetate
µl: Microliter
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
SNP: Single nucleotide polymorphism
ER: Estrogen Receptor
PR: Progesterone receptor
HER2: Humen Epidermal Growth Factor Receptor

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