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Impact of CYP2C8 T>C rs10509681 Genetic Variation on Efficacy and Safety of Paclitaxel in Iraqi Women with Breast Cancer

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ABSTRACT

Background: Breast cancer is the leading cause of cancer mortality among Iraqi women, accounting for approximately 34.35% of all cancer-related deaths in this demographic. Paclitaxel is an antineoplastic medication that stabilizes microtubules and is extensively utilized in the treatment of various malignancies, including breast cancer. This study aimed to investigate the genetic variation in metabolizing enzyme CYP2C8 T>C (rs10509681) and evaluate the impact of this variation on the efficacy and safety of paclitaxel in Iraqi women with breast cancer.

Methods: This cross-sectional observational study involved 150 women diagnosed with breast cancer who were administered paclitaxel. During the second week of paclitaxel therapy, these women were evaluated individually using a questionnaire to gather demographic information, such as age and body mass index, as well as the likelihood and intensity of paclitaxel's adverse effects. Simultaneously, neutrophilia levels and breast cancer biomarkers (CA15.3 and CEA) were evaluated.

Results: The wild-type TT was detected in about 69% of breast cancer cases, with the mutant type CC and the heterozygous type TC detected in about 10% and 21% of the cases, respectively. A significant association was found between the TT, TC, and CC genotypes and levels of the tumor markers CA 15-3 and CEA, as well as paclitaxel-related adverse effects (neutropenia, oral mucositis, peripheral neuropathy) in Iraqi breast cancer patients ($P < 0.05$).

Conclusion: Despite the small sample size and single-center design, the findings suggest that identifying the CYP2C8 T>C (rs10509681) genetic variations can impact treatment decisions in patients with breast cancer.

INTRODUCTION

Breast cancer (BC) is the most frequent malignancy in women, accounting for one in four cases among women, and is a heterogeneous disease on the molecular level.[1] Among Iraqi women with cancer, it is the leading cause of cancer death, accounting for approximately 34.35% of total cases.[2] Many factors contribute to the incidence of BC, including genetic inheritance, ecological factors, senescence, life pattern, and dietary influences. Accounting for this heterogeneity, cancer management concepts have evolved over the past decade to enhance therapeutic outcomes and minimize the adverse effects of chemotherapy.[3] BC is frequently monitored using markers, mainly cancer antigen (CA15-3) and Carcinoembryonic antigen (CEA), to detect progression and assess BC chemotherapy responsiveness.[4,5]

Cytochrome P450 (CYP) enzymes are monooxygenases that participate in the metabolism of both endogenous and exogenous substances.[6]

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CYP2C8, a crucial liver enzyme, exhibits a T>C (rs10509681) mutation that modifies its activity, hence affecting the metabolism and efficacy of drugs, including anticancer, antidiabetic, and antimalarial medications.[7] The CYP2C8*3 allele (R139K and K399R) increases the metabolism of medications such as pioglitazone and rosiglitazone.[8] Paclitaxel (PTX), a member of the taxane class, is an antineoplastic medication that stabilizes microtubules and is extensively utilized in the treatment of various malignancies, including BC.[9] Chemoresistance to taxanes, whether administered alone or in combination with biological agents, is a significant factor in treatment failure across many carcinomas and poses a critical challenge in oncology.

This issue impairs patient recovery and significantly diminishes the survival rate. The majority of the patients exhibit acquired resistance during chemotherapy or demonstrate primary resistance, characterized by an initial absence of therapeutic response.[10] This resistance was studied by many researchers who investigated the role of the cytochrome P450 system in metabolizing PTX and is critical for managing breast cancer, since some women on PTX therapy suffered from metastasis.[11] The adverse effects of PTX include alopecia, hypersensitivity reactions, nausea, emesis, bone marrow suppression, neutropenia, leukopenia, anaemia, arthralgia, myalgia, mucositis, asthenia, and neuropathy.

The significant adverse effects and drug resistance associated with PTX have prompted researchers to endeavour to mitigate these consequences. The intensity of these side effects may correlate with reduced efficacy of PTX.[12] PTX is predominantly metabolized by CYP2C8, yielding 6-hydroxypaclitaxel.[13] This study aimed to investigate the CYP2C8 (T>C; rs10509681) genetic variant and assess its impact on the efficacy and safety of PTX therapy in Iraqi women with BC.

METHODS

Patients

We recruited Iraqi women with postmenopausal status diagnosed with BC according to the National Comprehensive Cancer Network (NCCN) clinical practice guideline.[14] These women were randomly recruited from the oncology department of Imam Al-Hussein Medical City after obtaining consent.

Inclusion criteria

Women aged 50-78 years old received PTX as monotherapy at 80 mg/m², administered as a 1-hour intravenous infusion every week for at least two cycles, with no other concurrent diseases. The patients were included only if their medical records were available.

Exclusion criteria

Exclusion criteria comprised premenopausal women diagnosed with breast cancer (BC); patients with a history of cardiovascular disease, diabetes mellitus, hepatic dysfunction, or hyperthyroidism; and patients taking medications known to affect the pharmacokinetic or pharmacodynamic properties of paclitaxel (PTX), such as ketoconazole, erythromycin, rifampin, phenytoin, abaloparatide, abametapir, abatacept, and abciximab.

Study design

This cross-sectional observational study was conducted from December 2024 to March 2025 and involved 150 women with BC who received PTX. These women were assessed individually in the second week of PTX therapy using a questionnaire to obtain demographic data, including age and body mass index (BMI), and the probability and severity of PTX's side effects. At the same time, neutrophilia count and BC markers were assessed.

Blood collection

Approximately 6 mL of blood was withdrawn from each patient and divided into two parts: 2 mL was placed in an EDTA tube for the absolute neutrophil count and genetic analysis, and 4 mL was placed in a gel tube for serum collection to assess BC markers.

Measurement of breast cancer markers

The serum CA15.3 and CEA levels were measured using the chemiluminescent microparticle immunoassay technology[16] with the aid of the ARCHITECT i1000SR immunoassay analyzer and CA15.3 and CEA kits (Abbott, USA).

White blood cell count

Differential complete blood count was performed to assess haematological parameters, particularly the ANC, a critical indicator of bone marrow function and chemotherapy-induced myelosuppression in BC patients receiving PTX therapy. This test was performed using an automated Swelab Alfa Haematology Analyser (Boule Diagnostics AB, Sweden).

Assessment of the severity of paclitaxel-induced neutropenia

The severity of PTX-induced neutropenia is commonly graded using a scale derived from the National Cancer Institute Common Toxicity Criteria. This scale grades neutropenia into four scores based

on the ANC: score 1, ANC of ≥ 1.5 to <2×10^9/L; score 2, ANC of ≥1.0 to <1.5×109/L; score 3, ANC of ≥0.5 to < 1.0×109/L; and score 4, ANC <0.5×109/L.[17]

Assessment of paclitaxel-induced oral mucositis

The PTX-induced oral mucositis was assessed using the World Health Organization (WHO) scale, which combines both clinical and functional/symptoms-based examination. Oral mucositis was graded on a 5-point scale: 0, no oral mucositis; 1, erythema and soreness; 2, ulcers with ability to eat solids; 3, ulcers requiring a liquid diet; 4, ulcers with alimentation not possible.[18]

Assessment of paclitaxel-induced peripheral neuropathy

The severity of paclitaxel (PTX)-induced peripheral neuropathy was graded according to the WHO Common Toxicity Criteria for Peripheral Neuropathy. The criteria utilize a 5-grade scale: 0 (none), 1 (mild paresthesia and/or loss of reflexes), 2 (moderate paresthesia and/or mild objective weakness), 3 (severe or intolerable paresthesia and/or marked motor impairment), and 4 (life-threatening or paralysis).[19]

Genotyping

Genomic DNA was isolated from whole-blood samples using the AddPrep™ Genomic DNA Extraction Kit (AddBio, Korea) following the manufacturer's instructions. The allele-specific PCR (AS-PCR) method was utilized to identify CYP2C8 (rs10509681) gene polymorphisms, employing the Mastercycler Gradient Thermal Cycler (Eppendorf, Germany). This is a widely used SNP genotyping. It offers superior specificity and is cost-effective in distinguishing alleles based on single-nucleotide variations.[20] For each SNP, two allele-specific reverse primers (one for each allele) and one common forward primer were built according to Dr Hassan Abo Almaali. The primer sequences for this gene are forward 5-'GAAGACAGGGTGCTCTGGA-3' and reverse (Allele T) 5'-TCCGTGCTACATGATGACAA 3', and (Allele C) 5'-TCCGTGCTACATGATGACAG-3`, with a product size of 821 bp. Each PCR reaction was conducted in a total volume of 25 µL, comprising 3 µL of DNA template, 2 µL of each forward and reverse primer, 5 µL of 5× Master Mix (AddBio, Korea), and 13 µL of distilled water. The PCR parameters for rs10509681 included a duplicate run, with an initial denaturation at 95 °C for 5 minutes, followed by 35 cycles comprising 25 seconds at 95 °C, 25 seconds at 55 °C for annealing, and 1 minute at 72 °C, culminating in a final extension at 72 °C for 5 minutes. After amplification, 5 µL of each PCR product was combined with 3 µL of loading dye and applied to a 1.5% agarose gel prepared with 1× TBE buffer and 0.5 µg/mL ethidium bromide. Electrophoresis was conducted at 100 V for 35 minutes. DNA bands were visualised under UV light with a transilluminator and photographed using a digital camera. Band sizes were estimated by comparing them to a 100–1000 bp DNA ladder. Two independent evaluators validated all outcomes.

Statistical analysis

The Statistical Package for the Social Sciences (SPSS 26) was used to perform statistical analysis. The Shapiro–Wilk test was used first to assess the normality of data distribution, guiding subsequent test selection. For normally distributed numerical data, results are reported as mean and standard deviation (Mean ± SD). For non-normally distributed data, including BC markers, data are presented as median and interquartile range (Median ± IQR) and analyzed with nonparametric tests, specifically the Kruskal-Wallis test with post hoc-Dunn's test. Non-numerical (categorical) data, including PTX-related adverse effects, are presented as counts and percentages, and analyzed using the Chi-square test. The allele distribution of the CYP2C8 T>C genes was analysed with the Hardy-Weinberg equation and tested using nonparametric tests as well as the Chi-square test. Bivariate correlation – Pearson test was employed to assess the association of CYP2C8 C>A/T rs11572080 genetic variation with the efficacy and safety of PTX. A p-value less than 0.05 was considered statistically significant.

RESULTS

Demographic data of women with breast cancer

The mean age and BMI of women with BC were found to be 52.02 years ± 10.66 and 29.36 Kg/m^2 ± 5.15, respectively.

The serum level of breast cancer markers

The serum levels of BC markers were measured to investigate the efficacy of PTX, and the medians of these markers (CA 15.3 and CEA) were about 17.95 U/ml and 2.37 ng/ml, respectively.

The frequency and severity of paclitaxel-related adverse effects

The neutropenia induced by PTX was observed in varying severities in all BC women, with score 3 being predominant. The mucosa erythema, soreness, and difficulty eating were common characteristics of oral mucositis observed in most women with BC treated with PTX, and scores 1 and 2 were highly prevalent among those patients. Scores 1 and 2 of

peripheral neuropathy, characterised by paraesthesia, weakness, and reduced tendon reflexes, were commonly diagnosed in women with BC who were treated with PTX, as presented in Table 1.

Effects of CYP2C8 T>C genetic variation on breast cancer markers

The serum levels of BC markers, including CA 15.3 and CEA, were measured to investigate the effect of different CYP2C8 T>C genotypes on the PTX efficacy. The serum levels of CA 15.3 were significantly lower in Iraqi women with BC, who carried either the CC or TC genotypes compared to those with the TT genotype, at $P < 0.05$.

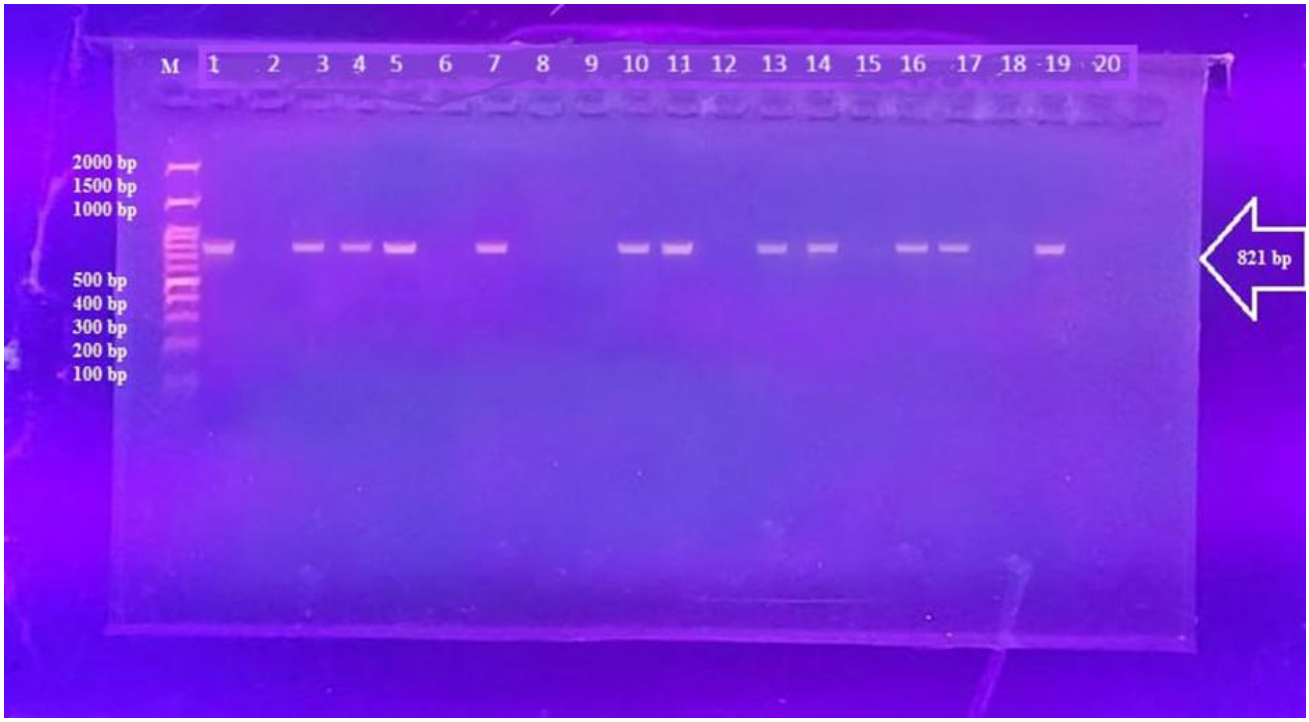

Figure 1. Gel electrophoresis image of PCR products showing the amplified 821 bp fragment of the CYP2C8 gene T>C (rs10509681), lanes 1 and 2 represent the TT allele, lanes 3 and 4 represent the TC allele, and lanes 9 and 10 represent the CC allele

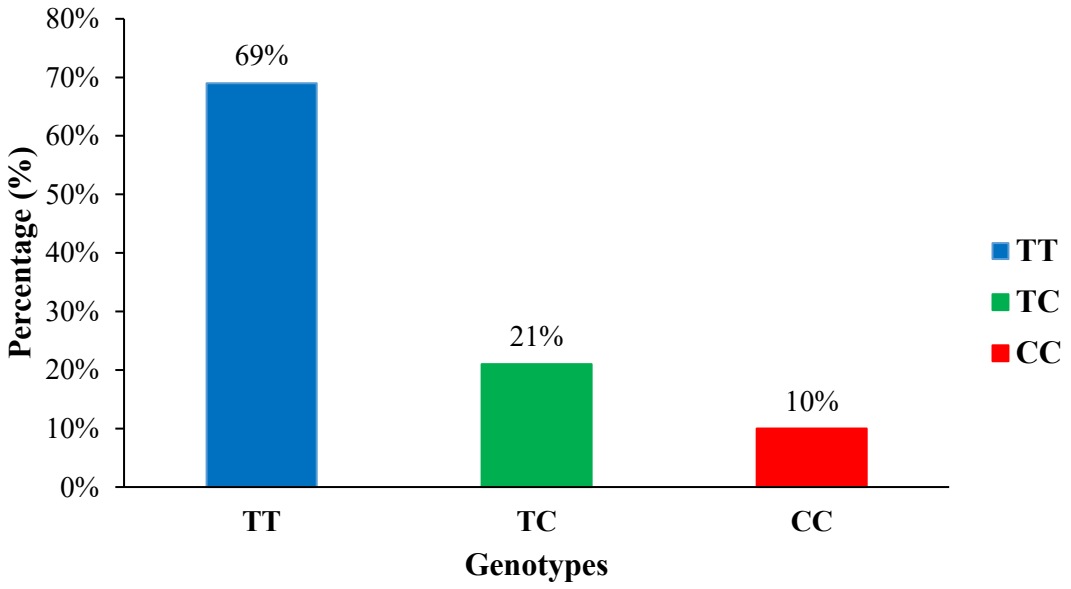

Figure 2. The prevalence of CYP2C8 T>C (rs10509681) genotypes among breast cancer patients

Table 1. The frequency and severity of PTX-related adverse effects

Paclitaxel-related adverse effects		No (%)
Neutropenia	Score 1	25 (16.6%)
	Score 2	24 (16%)
	Score 3	82 (54.7%)
	Score 4	19 (12.7%)
	Score 0	32 (21.4%)
Oral mucositis	Score 1	50 (33.3%)
	Score 2	59 (39.3%)
	Score 3	9 (6%)
	Score 4	0 (0%)
	Score 0	9 (6%)
Peripheral neuropathy	Score 1	70 (46.7%)
	Score 2	55 (36.7%)
	Score 3	13 (8.6%)
	Score 4	3 (2%)

Data expressed as No (%)

The serum levels of CEA were also significantly lower in women who carried either the TT or TC genotype compared to those with the CC genotype, at $P < 0.05$, as shown in Table 3. There was a significant association between the CYP2C8 T>C genetic variation and the serum level of BC markers, as explained in Table 4.

Effects of CYP2C8 T>C genetic variation on paclitaxel-related adverse effects

The high frequency of PTX-related adverse effects, including neutropenia, oral mucositis, and peripheral neuropathy, was assessed to identify the possible impacts of different CYP2C8 T>C genotypes on the PTX safety.

Table 2. The allele distribution of CYP2C8 T>C (rs10509681) in women with breast cancer

Genotype (N:150)	Frequency (%)	Allele	Frequency	Chi-square value	P-value
TT (wild type)	104 (69%)	T	0.8	19.68	<0.001
TC (heterozygous type)	31 (21%)	C	0.2		
CC (homozygous type)	15 (10%)				

The frequency of neutropenia was significantly higher in women carrying either the TC or CC genotype compared to those with the TT genotype, and scores 3 and 4 were commonly observed in these women at $P < 0.05$. This indicates an increase in the concentration of PTX in the blood due to impaired CYP2C8-mediated drug metabolism. This suggests that PTX affects neutrophil proliferation. Oral mucositis in scores 2 and 3 appeared more frequently in women with either the TC (53%) or CC (72%) genotype compared to those with the TT (28%) genotype at P<0.05.

Table 3. Serum levels of breast cancer markers according to the CYP2C8 T>C genetic variation

Parameters	Alleles of CYP2C8 T>C genotypes			P–value
	TT (No: 104)	TC (No: 31)	CC (No: 15)	
CA 15.3 (U/ml)	19.75 ± 20.1	18.6 ± 15.9*	14.2 ± 11.8*	0.005
CEA (ng/ml)	2.96 ± 3.48	1.64 ± 1.41	1.82 ± 1.07#	<0.001

Kruskal-Wallis – post hoc - Dunn's test, two-sided P-value <0.05, data expressed as median ± IQR, *: significant effect compared to TT genotype, #: significant effect compared to TT and TC genotypes.

Scores 3 and 4 of peripheral neuropathy were significantly more common in women with either the TC or CC genotype compared to those with the TT genotype at $P < 0.05$, as shown in Table 5. There was a significant association between the CYP2C8 T>C genetic variation and the frequency of neutropenia and oral mucositis, as indicated in Table 6.

Table 4. The correlation of the CYP2C8 T>C genotypes and breast cancer markers

Variables	Descriptive	CYP2C8 genotypes	CA 15.3	CEA
CYP2C8 genotypes	Pearson Correlation			
	P-value			
CA 15.3	Pearson Correlation	-0.152		
	P-value	0.063		
CEA	Pearson Correlation	-0.325*	-0.049	
	P-value	<0.001	0.553	

Bivariate correlation – Pearson test, two-sided *: Correlation is significant at the 0.01 level.

Table 5. Frequency and severity of paclitaxel-related adverse effects according to CYP2C8 T>C genetic variation.

Adverse effects		Alleles of CYP2C8 T>C genotypes			*P* – value
		TT (No: 104)	TC (No: 31)	CC (No: 15)	
Neutropenia	Score1	24 (23.1%)	1 (3.2%)	0 (0%)	<0.001
	Score 2	24 (23.1%)	0 (0%)	0 (0%)	
	Score 3	56 (53.8%)	18 (61.3%)	7 (46.7%)	
	Score 4	0 (0%)	11 (35.5%)	8 (53.3%)	
Oral mucositis	Score 0	32 (30.8%)	0 (0%)	0 (6.7%)	<0.001
	Score 1	43 (41.3%)	4 (12.9%)	3 (20%)	
	Score 2	29 (27.9%)	22 (71.9%)	8 (53.3%)	
	Score 3	0 (0%)	5 (16.1%)	4 (26.7%)	
	Score 4	0 (0%)	0 (0%)	0 (0%)	
Peripheral neuropathy	Score 0	9 (8.7%)	0 (0%)	0 (0%)	<0.001
	Score 1	54 (51.9%)	10 (32.3%)	6 (40%)	
	Score 2	37 (35.6%)	14 (45.3%)	4 (26.7%)	
	Score 3	4 (3.8%)	6 (19.2%)	3 (20%)	
	Score 4	0 (0%)	1 (3.2%)	2 (13.3%)	

Chi-square test, two-sided P-value <0.05, data expressed as N (%)

DISCUSSION

Cancer is one of the most common diseases around the world and the second leading cause of death after cardiovascular disease. BC is the most prevalent cancer type among Iraqi women, as it represents the highest percentage of malignant tumors in women.[21] PTX is frequently used as the first-line treatment drug in BC. Unfortunately, the resistance of BC to PTX treatment is a great obstacle in clinical applications and one of the major causes of death associated with treatment failure.[22] CYP2C8 primarily metabolizes PTX by converting it to 6-hydroxypaclitaxel. The genetic polymorphisms of CYP2C8, mainly CYP2C8*3, were reported to slow the clearance of many drugs, including PTX, thus enhancing the medicine`s pharmacological actions.[23]

Table 6. The correlation of the CYP2C8 T>C genotypes and PTX-related adverse effects.

Variables	Descriptive	CYP2C8 genotypes	Neutropenia	Oral mucositis	Peripheral neuropathy
CYP2C8 genotypes	Pearson Correlation				
	P-value				
Neutropenia	Pearson Correlation	0.525*			
	P-value	<0.001			
Oral mucositis	Pearson Correlation	0.527*	0.428*		
	P-value	<0.001	<0.001		
Peripheral neuropathy	Pearson Correlation	0.346*	0.269*	0.383*	
	P-value	<0.001	0.001	<0.001	

Bivariate correlation – Pearson test, two-sided *: Correlation is significant at the 0.01 level

The study showed that the CYP2C8 T>C (rs10509681) polymorphism was present in Iraqi women with BC, with the mutant type CC and the heterozygous type TC present in about 10% and 21%, respectively. The minor allele frequency of the C allele is significantly low (about 20%) in comparison to the reference major allele in selected women. In the Jordanian population, the prevalence of the CYP2C8 T>C (rs10509681) genetic polymorphism was significantly higher (4.3%) than in other East Asian populations. [23] The study involved a large sample size (411) of PTX-treated American populations with BC and found that most of the selected patients carried the TT genotype (80%) of the CYP2C8 T>C (rs10509681) gene, with the heterozygous genotype CT present in about 18% and the homozygous mutant genotype CC in a small number, about 1% [24] The CYP2C8 T>C (rs10509681) genetic variation is found at allele frequencies of 10-12% in Europeans, 2-12% in Africans, and much higher frequencies in specific populations like the Amish (15.2%) and Mossi of Burkina Faso (23.4%). This variation, which can alter the activity of the CYP2C8 enzyme, leads to differences in drug metabolism and underscores the need for population-specific pharmacogenetic profiles to guide precision medicine. [25]

In this study, the serum levels of BC markers (CA 15.3 and CEA) were adjusted within normal values in most Iraqi women with BC. This revealed that PTX effectively prohibited the metastasis. CA 15.3 and CEA were frequently performed for investigating, treatment monitoring, and advancing BC. If the result

value of CA 15.3 and CEA are ≥ 20 U/ml and 3 µg/L, respectively, this cancer is poorly responsive to therapy. [26] The study confirmed that the CYP2C8 T>C (rs10509681) genetic variation plays a significant role in determining the efficacy of PTX against BC in Iraqi women. So, women with one or two C alleles had low serum levels of BC markers (CA 15.3 and CEA) in comparison to those with paired T alleles. This study is consistent with other studies reporting that genetic polymorphism of CYP2C8 T>C reduced PTX metabolism, thereby enhancing the therapeutic response. [27, 28] The CYP2C8 gene encodes the CYP2C8 enzyme, a pivotal component of the CYP P450 system responsible for hepatic metabolism of various drugs, including PTX. [29] The CYP2C8*3 genetic polymorphism alters PTX clearance, potentially leading to higher serum levels and improved efficacy of PTX. [30] Another study in Turkey found that SNPs in the CYP2C8*3 gene (rs11572080 and rs10509681), which reduce PTX metabolic activity, lead to increased drug exposure and are associated with a probable increase in neuropathy risk. This study assessed the correlation of the specified gene with clinical outcomes and toxicity in 111 breast cancer patients. Patients possessing the CYP2C8*3 genotype exhibited a significantly higher rate of clinically complete response to neoadjuvant PTX (55% vs 23%; OR: 3.92, 95% Confidence Interval: 1.46–10.48, adjusted P-value: 0.046). [31]

This study demonstrated a robust correlation between the CYP2C8 T>C genetic polymorphism and the severity of PTX-related side effects. Women possessing one or two C alleles experienced considerably greater frequency of score 4 neutropenia compared to those with only T alleles. Green *et al.* discovered that individuals carrying the CYP2C8-HapC variation had an elevated risk of neutropenia. [32] Prolonged exposure to PTX induces myelosuppression by impairing the bone marrow's capacity to generate new blood cells, impacting hematopoietic stem and progenitor cells, and resulting in decreased neutrophils, erythrocytes, and platelet counts. This may elevate the risk of infection. [33] Oral mucositis in scores 2 and 3 was significantly more prevalent among Iraqi women with CC or TC genotypes at CYP2C8 T>C, indicating that elevated levels of PTX disrupt the rapid cellular turnover in the oral mucosa, resulting in diminished cell regeneration and inflammation. The research examined the prevalence and distribution of oral mucositis caused by chemotherapy drugs. Approximately 62.5% of patients receiving PTX exhibited oral mucositis symptoms. [34] Peripheral neuropathy was notably prevalent among Iraqi women possessing the minor allele of the CYP2C8 T>C genetic variant, with 3.2% to 20% of carriers experiencing scores 3 and 4 peripheral neuropathy. Alvarado *et al.* indicated that the CYP2C8*3 genetic polymorphism is linked to a moderate incidence of peripheral neuropathy produced by PTX and docetaxel. [35]

Limitations

We acknowledge that the cross-sectional observational design limits our ability to establish causal relationships between genotype and treatment response. We were unable to collect additional variables, which may limit our analysis.

CONCLUSION

The CYP2C8 T>C (rs10509681) genotype was markedly frequent among Iraqi women with BC, demonstrating a robust association with the efficacy and safety of PTX. Future cohort studies with larger sample sizes and pharmacokinetic evaluations, encompassing plasma PTX and metabolite concentrations, are advised to validate and elucidate this association.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

ETHICAL CONSIDERATIONS

This study was approved by the Scientific and Ethical Committee at Kerbala University, College of Pharmacy (Approval No: 2024HU11) and by the Kerbala Health Department, Iraqi Ministry of Health (Approval No: 432).

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DATA AVAILABILITY

All data generated or analyzed are included in the study.

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AI DISCLOSURE

This manuscript was not created using any generative AI methods for design, analysis, or writing.

AUTHOR CONTRIBUTIONS

H.H. participated in the study's design and execution, analysis of the results, and composition of the manuscript. A.A. contributed to the review and editing of the study and supervised the research. A.S. contributed to data collection and critically appraised the manuscript.

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