RESEARCH ARTICLE

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Genetic Polymorphisms of DNA Repair Genes and their Influence on Paclitaxel based Chemotherapy Induced Toxicity Reactions in Breast Cancer Patients

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Abstract

Background: Systemic chemotherapy constitutes an indispensable component of breast cancer (BC) management, where therapeutic drug combinations such as anthracyclines, platinum compounds, and taxanes form the cornerstone of standard treatment protocols. Although DNA repair genes are pivotal in cancer susceptibility, their specific roles in mediating acute or chronic toxicity outcomes induced by chemotherapy remain undetermined. Consequently, this study was planned to elucidate the impact of polymorphisms in base excision repair (*BER*) genes, including *XRCC1, XRCC2, XRCC3, APE1*, and *hOGG1*, on treatment response and toxicity outcomes in BC patients undergoing paclitaxel and doxorubicin-based chemotherapy within an Indian population**. Methods:** One hundred and four (104) BC patients receiving combined paclitaxel and doxorubicin chemotherapy were enrolled with documentation of both hematological and non-hematological toxicity reactions induced by the treatment. Genetic polymorphism of *XRCC1, XRCC2, XRCC3, APE1*, and *hOGG1* genes was investigated using Polymerase Chain Reaction (PCR) and Restriction Fragment Length Polymorphism (RFLP) analysis. **Results:** Analysis of the demographic characteristics of BC patients revealed a significant association between mucositis and peripheral neuropathy with advancing age. An increased body mass index was also significantly correlated with hematological toxicities, such as neutropenia (p=0.022) and febrile neutropenia (p=0.048), as well as with peripheral neuropathy (p=0.001). Univariate logistic regression analysis demonstrated a significant association between the *XRCC3* (*Ser241Cys*) polymorphism and peripheral neuropathy (OR=3.00, 95% CI: 1.29-6.95; p=0.010). Similarly, regression analysis indicated a significant association of *APE-1* (*Asp148Glu*) polymorphism with febrile neutropenia (OR=3.55, 95% CI: 1.03-12.21; p=0.044) and chemotherapy-induced nausea and vomiting (CINV) (OR=4.19, 95% CI: 1.61-10.94; p=0.003) in BC patients treated with paclitaxel and Doxorubicin regimen. **Conclusion:** The findings from this study underscore the significant influence of genetic polymorphisms in *XRCC3* (*Ser241Cys*) and APE-1 (Asp148Glu) on the acute toxicity effects induced by paclitaxel in BC patients.

Keywords: Breast cancer- genetic polymorphism- *XRCC1- XRCC2- XRCC3- APE-1- hOGG1*- Chemotherapy-toxicity

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Introduction

Breast cancer (BC) is the most common concern among women in both developing and developed countries and it ranks as the second leading cause of cancer-related deaths in women globally. Global cancer statistics showed that the overall burden of BC incidence and deaths is rising rapidly and that by 2040 there will be about 2964, 197 new BC cases with 31 % increase from 2,261,419 in year 2020 (11.7%) across the world [1]. BC is recognized as the principal and prominent cause of cancer related mortality in India, accounting 216,108 new cases (13.5 %) in 2022, with projections indicating a rise to 232, 832 cases by the year 2025 [2]. BC is a heterogeneous and multifactorial disease, wherein both established environmental factors and genetic determinants are scrutinized for their contributory roles in the pathogenesis of breast malignancy [3-4]. Numerous genetic and epigenetic modifications in DNA repair, tumor suppressor pathway genes contribute to increased risk of BC [5]. Genetic alterations of the genomic determinants resulted into uncertainty in normal cellular homeostasis, uninhibited cell growth, tumor development and finally in due course resulted into tumorigeneic process. The therapeutic approach to

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BC includes surgery, radiotherapy, hormone therapy, chemotherapy, targeted therapy, and immunotherapy. The best approach is chosen based on the type and stage of cancer, patient characteristics, and molecular features. Systemic chemotherapy in the form of adjuvant and neo-adjuvant chemotherapy has become an invasive treatment in BC management alongside surgery or radiotherapy, and is frequently used to improve the treatment outcomes [6-7]. Systemic treatment regimen plays a significant role in BC management wherein combinations of chemotherapy drugs with anthracyclines (Doxorubicin, Epirubicin), platinum (Cisplatin, Carboplatin) and taxanes (Paclitaxel, Docetaxel) forming the backbone of most schedules have been widely adopted in the standard therapeutics of BC [8-10].

Paclitaxel is a tetracyclic diterpenoid chemotherapeutic agent, utilized either alone [11-12] or in combination with other chemotherapy drugs to effectively treat advanced cancers. The paclitaxel treatment in combinations with cisplatin is documented in cervical cancer [13] head and neck cancer [14], carboplatin in gastric or esophageal cancer [15]. Almost all chemotherapy agents including paclitaxel can cause severe aftereffects (acute toxicities) in patients where haematological and non-hematological adverse reactions are prominent [16-19]. The most prevalent toxicities such as, alopecia, nausea and vomiting, mucositis, neutropenia, leukopenia, anemia, hypersensitivity reactions, arthralgia, myalgia, and peripheral neuropathy are caused by paclitaxel. Despite recent advances, predicting the outcomes of paclitaxel chemotherapy cannot be generalized for all patients. This is because paclitaxel-treated cells may upregulate DNA repair mechanisms, allowing them to repair drug-induced DNA damage and survive the toxic effects. Genetic polymorphisms affecting DNA repair capacity can influence the efficacy and toxicity of chemotherapy drugs. There are reports on the influence of *BER* gene polymorphisms on platinum and gemcitabine-based chemotherapy response in non-small cell lung cancer patients [20-23]. The *XRCC1* rs25487 and rs1799782 SNPs have been studied for their effectiveness in hematological toxicities in response to platinum based chemptherapy in NSCLC [24] esophagus [25] and colorectal cancer [26]. However, evidence on the association of DNA repair gene polymorphisms with treatment outcomes in BC patients treated with paclitaxel alone or in combination with other drugs, has not been established. It was assumed that genetic variability in DNA repair pathway genes might be connected to chemotherapy-induced toxicity reactions in BC patients receiving paclitaxel chemotherapy. Understanding the pharmacogenetic susceptibility of patients with genetic variants in DNA repair genes is crucial for assessing their role in drug toxicity profiles. This brings into interest to explore the genetic control of DNA repair genes on normal tissue during paclitaxel chemotherapy in BC patients. Therefore, in this study, we decided to verify association of single nucleotide polymorphisms (SNPs) of DNA repair genes and their impact on treatment related outcomes including toxicities in BC patients treated with paclitaxel based chemotherapy. To address this, we investigated the polymorphisms of *XRCC1* (Arg194Trp, Arg280His, Arg399Gln), *XRCC2* (Arg188His), *XRCC3* (Ser241Cys), *APE-1* (Asp148Glu), *hOGG1* (Ser326Cys) genes and their association with chemotherapy induced toxicity reactions in BC patients from Maharashtra.

Materials and Methods

Study Design

Cross-sectional, Observational,Analytical study was carried out at Department of Molecular Biology and Genetics in association with Department of Oncology of Krishna Hospital and Medical Research Center, Karad, Maharashtra, India.

Patient enrollment and clinical information

One hundred and four (104) patients with histologically confirmed non-metastatic breast cancer, visiting to Krishna Hospital and Medical Research Centre for the treatment at Department of Oncology of Krishna Vishwa Vidyapeeth (Deemed to be Univesrsity) Karad were enrolled in this study. Patients were enrolled in this study based upon selection criterias including; histopathological confirmation, no metastasis. The patients with no pathological diagnosis, incomplete treatment, incomplete followup, patients with other comorbidities were excuuded from the study. This detailed clinical profile encompassing with demographic characteristics, chemotherapy regimens, and follow-up details, was systematically recorded.

Chemotherapy treatment regimen follow up and toxicity assessment

Upon enrollment the patients were administered with four cycles of paclitaxel every three weeks thereafter four cycles of Doxorubicn. After the first cycle of chemotherapy, patients were monitored between Day 10 and Day 14 for chemotherapy-related toxicities. The patients were followed for one year at regular intervals to assess treatment response and toxicity. Patients were informed about potential adverse effects and advised to report any serious side effects or attend scheduled follow-ups, with these incidents graded per the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 4.03. Patients were routinely tested for blood and urine parameters, including complete blood count, renal function, and liver function before each chemotherapy cycle, to monitor health and identify chemotherapy-induced side effects. Both hematological toxicities (e.g., anemia, neutropenia) and non-hematological toxicities (e.g., mucositis, chemotherapy-induced nausea/vomiting (CINV), fatigue, body ache, peripheral neuropathy) were recorded and classified according to NCI-CTC criteria and graded from 0 to 4. For comparison of BC patients with toxicity reactions (>1 grade) were considered as chemo-sensitive groups and compared to patients with ≤ 1 grade reactions.

Blood sample collection, genomic DNA extraction and genotyping assays

Five milliliter (mL) of intravenous blood from

each patient 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. The genotyping assay of DNA repair genes *XRCC1*, *XRCC2, XRCC3, APE-1*, and *hOGG1* was conducted using PCR-RFLP method. The PCR amplification for polymorphism confirmation was performed in 20 µL reaction mixtures containing 1X PCR buffer, 0.2 mM each dNTP, 10 pmol each primer (IDT technologies), 1U Taq DNA polymerase (GeNei, Merck Bioscience), and 100 ng of purified genomic DNA. The primer sequence used to amplify *XRCC1* (Arg194Trp); forward primer (FP): 5'-GCC AGG GCC CCT CCT TCA A-3'; reverse primer (RP): 5'-TAC CCT CAG ACC CAC GAG T-3' *XRCC1* (Arg280His); FP:5'-CCA GCT CCA ACT CGT ACC-3'; RP: 5' ATG AGG TGC GTG CTG TCC-3', *XRCC1* (Arg399Gln); FP: 5'-CAG TGG TGC TAA CCT AAT C-3' ; RP: 5'-AGT AGT CTG CTG GCT CTG G-3, *XRCC2* (Arg188His); FP: 5'-GTT GCT GCC ATG CCT TAC A-3' ; RP: 5'-TGT AGT CAC CCA TCT CTC TGC-3', *XRCC3* (Ser241Cys); FP: 5'-GGT CGA GTG ACA GTC CAA AC-3' ; RP: 5'-TGC AAC GGC TGA GGG TCT T- 3', APE-1 (Asp148Glu; FP:5'-CTG TTT CAT TTC TAT AGG CTA-3'; RP:5'- AGG AAC TTG CGA AAG GCT TC-3', hOGG1(Ser326Cys); FP:5'- CTG TTC AGT GCC GAC CTG CGC CGA -3'; RP: 5' ATC TTG TTG TGC AAA CTG AC -3'. Subsequently, the PCR-amplified products of *XRCC1* (cd-194: 485 bp, cd-280: 257 bp, cd-399: 871 bp), *XRCC2* (cd-188: 290 bp), *XRCC3* (cd-241: 455 bp), *APE1* (cd-148: 164 bp), and *hOGG1* (cd-326: 247bp) were digested overnight with restriction enzymes PvuII, RsaI, NciI, HphI, NlaIII, BfaI, MboII respectively.The digestion reactions were then analyzed via agarose gel electrophoresis in Tris-Acetate-EDTA (TAE) buffer, stained with ethidium bromide (10 mg/mL), and visualized under a UV transilluminator. The results were subsequently photographed using a gel documentation system (BioRad Laboratories).

Statistical analysis

The Odds Ratio (OR) and corresponding 95% confidence intervals (CI) were calculated to determine the association between the grade of acute toxicity and selected gene polymorphisms. A univariate logistic regression model assessed the impact of each genetic polymorphism in DNA repair genes on the incidence of toxicity (grades 0-1 vs. 2-4), with results expressed as ORs and 95% CIs. The clinical severity of post-chemotherapy adverse effects was defined by hematological and non-hematological toxicity reactions exceeding grade 1. Statistical significance was set at $p < 0.05$, and all analyses were performed using SPSS Software (Version 21.0).

Results

Demographic, clinical characteristics and chemotherapy induced toxicities in study subjects

In this study, 104 BC patients were enrolled, with ages ranging from 27 to 78 years and a mean age of 50.30 years. Among these patients, 44 (42.31%) were over 50 years old, with 35 (66.35%) women having a BMI of ≤ 25, and 35 (33.65%) women having a BMI greater than 25. A total of 85 (81.73%) women received adjuvant chemotherapy, while 19 were treated with neoadjuvant chemotherapy. Immunohistochemical analysis revealed that 48 patients were ER/PR positive, 53 patients were ER/PR negative, and 44 patients had triple-negative breast cancer. Clinical TNM staging showed that 47 patients were at stage III or IV, and histopathological TNM staging indicated the same for another 47 patients. All 104 patients initially received Paclitaxel followed by Doxorubicin, and 43 patients were also administered Tamoxifen in conjunction with combined chemotherapy. After a one-year follow-up post-chemotherapy, 49 patients showed no evidence of disease, 35 patients experienced metastasis, four patients had a recurrence of the disease, and two patients succumbed to it. Significant hematological toxicities, including anemia (84.62%) with grade >1 toxicity, were observed following Paclitaxel chemotherapy, whereas neutropenia and febrile neutropenia did not show a significant increase. Notably, non-hematological toxicities with grade >1 were significantly elevated in patients treated with Paclitaxel. Chemotherapy-induced nausea and vomiting and fatigue were noted with grade >1 toxicity in 94.23% of patients, 85.58% experienced body ache with grade >1 toxicity, and 75.96% suffered from significantly higher rates of peripheral neuropathy.

The demographic, clinical, and histopathological characteristics were correlated with paclitaxel-based chemotherapy-induced toxicities in BC patients, revealing no association of anemia with age, BMI, or clinical and pathological TNM stages III and IV. However, non-hematological toxicities demonstrated a significant correlation with the age of BC patients over 50 years, where mucositis ($p=0.002$) and peripheral neuropathy ($p=0.009$) showed a marked increase. Analyzing the impact of BMI on chemotherapy-induced acute toxicities in patients treated with paclitaxel revealed a significant correlation of BMI >25 with hematological toxicities such as neutropenia ($p=0.022$) and febrile neutropenia ($p=0.048$), as well as peripheral neuropathy ($p=0.001$). The analysis of clinical TNM stage with grade >III indicated a significant association with mucositis ($p=0.047$), while histopathological TNM grade >III showed an association with neutropenia ($p=0.027$) in patients treated with the combination of paclitaxel and Doxorubicin chemotherapy.

Analysis of genotype distribution of XRCC1, XRCC2, XRCC3, APE-1 and hOGG-1 gene polymorphisms and paclitaxel induced toxicity effects in BC patients

The regression analysis of polymorphisms in DNA repair genes, including *XRCC1, XRCC2, XRCC3, APE-1*, and *hOGG1*, and their association with acute hematological and non-hematological toxicities induced by combined paclitaxel and Doxorubicin chemotherapy are detailed in Table 1 to Table 7. Hematological and non-hematological toxicities were classified into grade ≤1 or >1 based on NCI-CTC criteria. Among the 104 BC patients primarily treated with paclitaxel followed by

Table 1. Effect of Genetic Polymorphisms of DNA Repair Gene (*XRCC1, codon-194, exon-6*) on Risk of Paclitaxel Chemotherapy Induced Hematological and Non-Hematological Toxicity Reactions in Breast Cancer Patients

Toxicities	XRCC1 Genotypes	Toxicity Grade ≤1	Toxicity Grade >1	OR	(95% CI)	pvalue
Anemia	Arg/Arg	72	10	1 (Reference)		
	Arg/Trp	16	4	1.8	0.50-6.47	0.368
	Trp/Trp	2	0	1.38	0.06-30.79	0.838
	Arg/Trp+Trp/Trp	18	4	1.6	0.44-5.69	0.468
Neutropenia	Arg/Arg	71	11	1 (Reference)		
	Arg/Trp	18	2	0.71	0.14-3.52	0.682
	Trp/Trp	2	0	1.24	0.05-27.59	0.89
	Arg/Trp+Trp/Trp	20	2	0.64	0.13-3.15	0.588
Febrile neutropenia	Arg/Arg	71	11	1 (Reference)		
	Arg/Trp	19	1	0.33	0.04-2.79	0.315
	Trp/Trp	2	0	1.24	0.05-27.59	0.89
	Arg/Trp+Trp/Trp	21	1	0.3	0.03-2.52	0.271
Mucositis	Arg/Arg	37	45	1 (Reference)		
	Arg/Trp	12	8	0.54	0.20-1.48	0.236
	Trp/Trp	1	1	0.82	0.04-13.59	0.891
	Arg/Trp+Trp/Trp	13	9	0.56	0.21-1.47	0.247
CINV	Arg/Arg	60	23	1 (Reference)		
	Arg/Trp	14	5	0.93	0.30-2.88	0.902
	Trp/Trp	1	1	2.6	0.15-43.47	0.504
	Arg/Trp+Trp/Trp	15	6	1.04	0.36-3.01	0.937
Fatigue	Arg/Arg	58	24	1 (Reference)		
	Arg/Trp	15	5	0.8	0.26-2.46	0.704
	Trp/Trp	2	0	0.47	0.02-10.31	0.637
	Arg/Trp+Trp/Trp	17	5	0.71	0.23-2.14	0.544
Bodyache	Arg/Arg	43	38	1 (Reference)		
	Arg/Trp	12	9	0.84	0.32-2.23	0.739
	Trp/Trp	1	1	1.13	0.06-18.72	0.931
	Arg/Trp+Trp/Trp	13	10	0.87	0.34-2.21	0.77
Peripheral neuropathy	Arg/Arg	54	29	1 (Reference)		
	Arg/Trp	15	4	0.496	0.15-1.63	0.249
	Trp/Trp	1	4	7.44	0.79-69.77	0.078
	Arg/Trp+Trp/Trp	16	5	0.58	0.19-1.74	0.335

OR, Odds ratio; CI, Confidence interval; p value determined based on χ^2; Level of significance ($p< 0.05$)

Doxorubicin, 90 patients exhibited G1-G4 grade toxicities, while 14 patients displayed G0 grade anemia toxicity. Severe neutropenia (G1-G4) was observed in 28 patients, and febrile neutropenia (G1-G4) in 14 patients. Following paclitaxel chemotherapy, severe non-hematological toxicities with grade G1-G4 were noted in 56 patients with mucositis, 100 patients with chemotherapy-induced nausea and vomiting (CINV) and fatigue, 91 patients with body aches, and 81 patients with peripheral neuropathy. The univariate logistic regression analysis of genetic polymorphisms in the XRCC1 gene, specifically at codon 194 of exon 6, did not reveal any significant association with hematological or non-hematological toxicities in BC patients treated with paclitaxel chemotherapy (Table 1). Similarly, the Arg280His polymorphism of the *XRCC1* gene at exon 9 was not correlated with any hematological or non-hematological toxicity reactions, such as mucositis, chemotherapy-induced nausea and vomiting (CINV), body ache, or peripheral neuropathy (Table 2). No significant differences were observed in the incidence of severe toxicities, including mucositis, CINV, fatigue, and body ache, in Paclitaxel-treated breast cancer patients with the 280His genotype of the *XRCC1* gene. Furthermore, the *XRCC1* gene polymorphism at codon 399 of exon 10 did not show any significant correlation with hematological or non-hematological acute toxicities from Paclitaxel chemotherapy in BC patients (Table 3). In the analysis of the *Arg188His* polymorphism of the *XRCC1* gene and its association with paclitaxel-induced acute toxicities in BC patients, no significant association was found between genetic variants of the *XRCC2* gene and the development of increased acute hematological

Table 2. Effect of Genetic Polymorphisms of DNA Repair Gene (*XRCC1, cd-280,exon-9*) on Risk of Paclitaxel Chemotherapy Induced Hematological and Non-Hematological Toxicity Reactions in Breast Cancer Patients

Toxicities	*XRCC1* Genotypes	Toxicity Grade ≤1	Toxicity Grade >1	OR	(95% CI)	pvalue
Anemia	Arg/Arg	38	5	1 (Reference)		
	Arg/His	48	9	1.42	0.44-4.60	0.554
	His/His	4	0	0.77	0.03-16.51	0.871
	Arg/His+His/His	52	9	1.31	0.40-4.24	0.646
Neutropenia	Arg/Arg	40	4	1 (Reference)		
	Arg/His	48	8	1.66	0.46-5.94	0.431
	His/His	3	1	3.33	0.27-40.03	0.342
	Arg/His+His/His	51	9	1.76	0.50-6.14	0.372
Febrile neutropenia	Arg/Arg	39	4	1 (Reference)		
	Arg/His	50	7	1.36	0.37-4.99	0.638
	His/His	3	1	3.25	0.27-39.04	0.352
	Arg/His+His/His	53	8	1.47	0.41-5.23	0.55
Mucositis	Arg/Arg	43	0	1 (Reference)		
	Arg/His	51	6	10.98	0.60-200.49	0.105
	His/His	4	0	9.66	0.17-548.42	0.27
	Arg/His+His/His	55	6	10.18	0.55-185.87	0.117
CINV	Arg/Arg	30	13	1 (Reference)		
	Arg/His	43	14	0.75	0.30-1.82	0.527
	His/His	3	1	0.76	0.07-8.10	0.827
	Arg/His+His/His	46	15	0.75	0.31-1.80	0.523
Fatigue	Arg/Arg	32	12	1 (Reference)		
	Arg/His	40	16	1.06	0.44-2.57	0.885
	His/His	3	4	3.55	0.69-18.28	0.128
	Arg/His+His/His	43	17	1.05	0.44-2.51	0.905
Bodyache	Arg/Arg	23	21	1 (Reference)		
	Arg/His	29	27	1.01	0.46-2.24	0.961
	His/His	4	0	0.12	0.006-2.39	0.165
	Arg/His+His/His	33	27	0.89	0.41-1.95	0.782
Peripheral neuropathy	Arg/Arg	30	16	1 (Reference)		
	Arg/His	37	17	0.86	0.37-1.98	0.726
	His/His	3	1	0.62	0.06-6.50	0.694
	Arg/His+His/His	40	18	0.84	0.37-1.92	0.685

OR, Odds ratio; CI, Confidence interval; p value determined based on χ^2; Level of significance ($p< 0.05$)

or non-hematological toxicities from paclitaxel-based chemotherapy. The logistic regression analysis of *XRCC2* gene polymorphisms and their association with acute toxicities in BC patients following paclitaxel chemotherapy is presented in Table 4. The findings from the univariate regression analysis examining the association of the *XRCC3* gene *Ser241Cys* polymorphism at exon 7 with both hematological and non-hematological toxicities induced by paclitaxel-based chemotherapy in BC patients are detailed in Table 5. The odds ratios with 95% confidence intervals for patients with the combined heterozygous and recessive Ser/Cys + Cys/Cys genotypes indicated a significant association with peripheral neuropathy (OR=3.00, 95% CI: 1.29-6.95; p=0.010). However, the XRCC3 Ser241Cys polymorphism did not show any significant correlation with other hematological or non-hematological toxicities. Similarly, the ASP148Glu polymorphism of the *APE-1* gene was studied for its association with Paclitaxel-induced chemotherapy toxicity, yielding noteworthy results. There was a significant association of the heterozygous Asp/Glu genotype of APE-1 with febrile neutropenia (OR=3.55, 95% CI: 1.03-12.21; p=0.044) and chemotherapy-induced nausea and vomiting (OR=4.19, 95% CI: 1.61-10.94; p=0.003) in BC patients treated with paclitaxel chemotherapy (Table 6). Additionally, the *hOGG1* (*Ser326Cys*) polymorphism at codon 326 of exon 7, was assessed for its association with acute toxicities induced by paclitaxel chemotherapy, but this analysis showed no significant association with either hematological or non-hematological toxicities (Table 7).

Table 3. Effect of Genetic Polymorphisms of DNA Repair Gene (*XRCC1,cd-399, exon-10*) on Risk of Paclitaxel Chemotherapy Induced Hematological and Non-Hematological Toxicity Reactions in Breast Cancer Patients

Toxicities	*XRCC1* Genotypes	Toxicity Grade ≤1	Toxicity Grade >1	OR	(95% CI)	p value
Anemia	Arg/Arg	37	9	1 (Reference)		
	Arg/Gln	44	4	0.37	0.10-1.31	0.124
	Gln/Gln	8	2	1.02	0.18-5.69	0.975
	Arg/Gln+Gln/Gln	52	6	0.47	0.15-1.44	0.19
Neutropenia	Arg/Arg	41	6	1 (Reference)		
	Arg/Gln	41	7	1.16	0.36-3.77	0.796
	Gln/Gln	9	0	0.33	0.01-6.49	0.470
	Arg/Gln+Gln/Gln	50	7	0.95	0.29-3.07	0.941
Febrile neutropenia	Arg/Arg	41	7	1 (Reference)		
	Arg/Gln	41	5	0.71	0.20-2.43	0.591
	Gln/Gln	9	1	0.65	0.07-5.96	0.704
	Arg/Gln+Gln/Gln	50	6	0.70	0.21-2.25	0.553
Mucositis	Arg/Arg	45	2	1 (Reference)		
	Arg/Gln	43	5	2.61	0.48-14.21	0.265
	Gln/Gln	9	0	0.95	0.04-21.60	0.978
	Arg/Gln+Gln/Gln	52	5	2.16	0.40-11.69	0.370
CINV	Arg/Arg	31	16	1 (Reference)		
	Arg/Gln	36	12	0.64	0.26-1.57	0.335
	Gln/Gln	8	1	0.24	002-2.10	0.199
	Arg/Gln+Gln/Gln	44	13	0.57	0.24-1.35	0.205
Fatigue	Arg/Arg	34	13	1 (Reference)		
	Arg/Gln	35	13	0.97	0.39-2.39	0.949
	Gln/Gln	6	3	1.30	0.28-6.01	0.730
	Arg/Gln+Gln/Gln	41	16	1.02	0.43-2.41	0.962
Bodyache	Arg/Arg	26	22	1 (Reference)		
	Arg/Gln	22	24	1.28	0.57-2.89	0.539
	Gln/Gln	6	4	0.78	0.19-3.15	0.736
	Arg/Gln+Gln/Gln	28	28	1.18	0.54-2.55	0.671
Peripheral neuropathy	Arg/Arg	30	19	1 (Reference)		
	Arg/Gln	32	14	0.69	0.29-1.61	0.394
	Gln/Gln	7	2	0.45	0.08-2.40	0.351
	Arg/Gln+Gln/Gln	39	16	0.64	0.28-1.46	0.298

OR, Odds ratio; CI, Confidence interval; p value determined based on χ^2; Level of significance ($p< 0.05$)

Discussion

Genetic factors significantly influence an individual's susceptibility to chemotherapy-induced adverse reactions, and understanding these factors can aid in mitigating the side effects of chemotherapy. While chemotherapeutic agents are designed for target-specific actions, the mechanisms of many chemotherapy drugs remain inadequately understood. Therefore, comprehending the genetic diversity of patients undergoing chemotherapy is crucial, as it determines pharmacogenetic susceptibility to both the efficacy and toxicity of these drugs. A substantial number of patients experience severe acute or late toxicity reactions without clear justification for the severity. However, this unpredictability can largely be attributed to the genetic makeup of individuals, which may account for their clinical sensitivity to chemotherapy and negatively impact their quality of life. Numerous studies have indicated that genetic variability, particularly in genes involved in DNA repair pathways, is associated with chemotherapy-induced toxicity [22, 27-31]. Some SNPs of DNA repair genes have been elucidated for their role in therapeutic response to certain chemotherapy treatments. However, other SNPs might partially accounted for the interindividual variability observed in response to chemotherapeutic drugs [24, 32-33]. The toxicities related to chemotherapeutic drugs, which are associated with genetic polymorphisms in DNA repair genes, can provide valuable insights into predicting clinical responses and outcomes of selected chemotherapy regimens [34].

In this context, polymorphisms of *BER* genes, including *XRCC1* and *XRCC2*, have been extensively

Table 4. Effect of Genetic Polymorphisms of DNA Repair Gene (*XRCC2, cd 188, exon-3*) on Risk of Paclitaxel Chemotherapy Induced Hematological and Non-Hematological Toxicity Reactions in Breast Cancer Patients

Toxicities	*XRCC2* Genotypes	Toxicity Grade ≤1	Toxicity Grade >1	OR	(95% CI)	p value
Anemia	Arg/Arg	73	11	1 (Reference)		
	Arg/His	16	3	1.24	0.31-4.97	0.757
	His/His	0	0	NC		
	Arg/His+His/His	16	3	1.24	0.31-4.97	0.757
Neutropenia	Arg/Arg	71	11	1 (Reference)		
	Arg/His	21	1	0.31	0.03-2.52	0.271
	His/His	0	0	NC		
	Arg/His+His/His	21	1	0.31	0.03-2.52	0.271
Febrile neutropenia	Arg/Arg	72	11	1 (Reference)		
	Arg/His	20	1	0.32	0.03-2.68	0.298
	His/His	0	0	NC		
	Arg/His+His/His	20	1	0.32	0.03-2.68	0.298
Mucositis	Arg/Arg	77	5	1 (Reference)		
	Arg/His	21	1	0.73	0.08-6.52	0.782
	His/His	0	0	NC		
	Arg/His+His/His	21	1	0.73	0.08-6.52	0.782
CINV	Arg/Arg	63	21	1 (Reference)		
	Arg/His	12	8	2.00	0.71-5.55	0.183
	His/His	0	0	NC		
	Arg/His+His/His	12	8	2.00	0.71-5.55	0.183
Fatigue	Arg/Arg	60	23	1 (Reference)		
	Arg/His	15	6	1.04	0.36-3.01	0.937
	His/His	0	0	NC		
	Arg/His+His/His	15	6	1.04	0.36-3.01	0.937
Bodyache	Arg/Arg	44	39	1 (Reference)		
	Arg/His	12	10	0.94	0.36-2.41	0.898
	His/His	0	0	NC		
	Arg/His+His/His	12	10	0.94	0.36-2.41	0.898
Peripheral neuropathy	Arg/Arg	56	27	1 (Reference)		
	Arg/His	14	7	1.03	0.37-2.86	0.944
	His/His	0	0	NC		
	Arg/His+His/His	14	7	1.03	0.37-2.86	0.944

OR, Odds ratio; CI, Confidence interval; p value determined based on χ^2; Level of significance ($p< 0.05$)

studied for their significant associations with both the response and toxicity of chemotherapy [35]. Several studies have highlighted the influence of *XRCC1* gene (*Arg399Gln*) polymorphism on clinical outcomes in patients with colorectal cancer [36-37] and ovarian cancer [28] in response to platinum-based chemotherapy. Additionally, other studies have demonstrated an increased risk of chemotherapy-induced hematological toxicities in non-small cell lung cancer (NSCLC) patients harboring the *XRCC1* gene polymorphism when treated with platinum-based chemotherapy [22, 38-40]. Similarly, another study revealed a significant association between the XRCC1 (Arg399Gln) polymorphism and an elevated risk of hematological toxicities in NSCLC patients in response to a combination of cisplatin and gemcitabine chemotherapy [41]. Furthermore, the variant (Gln/Gln) genotype of the XRCC1 (Arg399Gln) polymorphism was associated with an increased risk of gastrointestinal toxicities in lung cancer patients treated with cisplatin-based chemotherapy [42].

However, other studies on DNA repair gene polymorphisms did not demonstrate any chemotoxic response in NSCLC [43] and pharyngeal cancer patients [44] when treated with platinum- or taxane-based chemotherapy. In a similar vein, XRCC1 Arg399Gln polymorphisms showed no association with chemotherapy-induced toxicities in lung cancer patients treated with cisplatin-based chemotherapy [42] and in NSCLC cases receiving a combination of platinum and paclitaxel or docetaxel-based chemotherapy [45]. Thus, numerous studies have delved into the genetic variations within these genes and their implications for cancer susceptibility;

Table 5. Effect of Genetic Polymorphisms of DNA repair Gene (*XRCC3, cd-241, exon-7*) on Risk of Paclitaxel Chemotherapy Induced Hematological and Non-Hematological Toxicities in Breast Cancer Patients

Toxicities	*XRCC3* Genotypes	Toxicity Grade ≤1	Toxicity Grade >1	OR	(95% CI)	p value
Anemia	Ser/Ser	55	6	1 (Reference)		
	Ser/Cys	32	7	2.00	0.61-6.48	0.245
	Cys/Cys	2	1	4.58	0.36-58.35	0.240
	Ser/Cys+Cys/Cys	35	8	2.09	0.67-6.55	0.203
Neutropenia	Ser/Ser	55	6	1 (Reference)		
	Ser/Cys	33	7	1.94	0.60-6.28	0.266
	Cys/Cys	2	1	4.58	0.36-58.35	0.240
	Ser/Cys+Cys/Cys	35	8	2.09	0.67-6.55	0.203
Febrile neutropenia	Ser/Ser	57	4	1 (Reference)		
	Ser/Cys	32	8	3.56	0.99-12.76	0.051
	Cys/Cys	3	0	1.82	0.08-41.11	0.704
	Ser/Cys+Cys/Cys	35	8	3.25	0.91-11.62	0.068
Mucositis	Ser/Ser	57	3	1 (Reference)		
	Ser/Cys	38	2	1.00	0.15-6.26	1.000
	Cys/Cys	4	0	1.82	0.08-41.11	0.704
	Ser/Cys+Cys/Cys	42	2	0.9	0.144-5.65	0.914
CINV	Ser/Ser	45	17	1 (Reference)		
	Ser/Cys	27	12	1.17	0.48-2.83	0.717
	Cys/Cys	2	1	1.32	0.11-15.56	0.823
	Ser/Cys+Cys/Cys	29	13	1.18	0.50-2.80	0.696
Fatigue	Ser/Ser	43	17	1 (Reference)		.
	Ser/Cys	29	12	1.04	0.43-2.51	0.918
	Cys/Cys	2	1	1.26	0.10-14.88	0.851
	Ser/Cys+Cys/Cys	31	13	1.06	0.45-2.49	0.892
Bodyache	Ser/Ser	31	28	1 (Reference)		
	Ser/Cys	23	19	0.91	0.41-2.02	0.825
	Cys/Cys	1	2	2.21	0.19-25.77	0.525
	Ser/Cys+Cys/Cys	24	21	0.96	0.44-2.10	0.936
Peripheral neuropathy	Ser/Ser	46	14	1 (Reference)		
	Ser/Cys	22	19	2.83	1.20-6.68	0.017*
	Cys/Cys	1	2	6.57	0.55-77.99	0.135
	Ser/Cys+Cys/Cys	23	21	3.00	1.29-6.95	0.010*

OR, Odds ratio; CI, Confidence interval; p value determined based on χ^2; Level of significance ($p< 0.05$); *, Indicates significant Odds Ratio ($p<0.05$)

however, there remains a paucity of information concerning SNPs in *BER* genes and their correlation with chemotherapy treatment responses and outcomes across a range of cancers, including BC. Consequently, it becomes imperative to identify genetic polymorphisms in critical DNA repair genes, such as *XRCC1, XRCC2, XRCC3, APE-1*, and *hOGG1*, to enhance the efficacy of chemotherapeutic interventions and mitigate the associated toxicity in BC patients.

Paclitaxel chemotherapy, when combined with Doxorubicin, is a standard treatment regimen for BC management. However, there are no reports on paclitaxel-related chemotherapy-induced toxicity reactions in BC or other cancer types. In this context, our study explored the association of genetic polymorphisms in BER genes with chemotherapy-induced toxicity reactions. The results demonstrated significant association between the combined heterozygous and recessive genotypes of the *XRCC3* (*Ser241Cys*) polymorphism and peripheral neuropathy in BC patients treated with paclitaxel and doxorubicin which was not reported earlier. Similarly, the heterozygous genotype of the *APE-1* gene polymorphism showed a significant positive influence on both hematological toxicity, such as febrile neutropenia, and non-hematological toxicity, such as chemotherapy-induced nausea and vomiting (CINV), in BC patients administered a combination of paclitaxel followed by doxorubicin. In contrast, our investigation found no significant correlation between the XRCC1 (Arg399Gln) polymorphism, as well as its variations at codons 194 and

Table 6. Effect of Genetic Polymorphisms of DNA Repair Gene (*APE1, cd-148, exon-5*) on Risk of Paclitaxel Chemotherapy Induced Hematological and Non-Hematological Toxicity Reactions in Breast Cancer Patients

Toxicities	APE-1 Genotypes	Toxicity Grade ≤1	Toxicity Grade >1	OR	(95% CI)	pvalue
Anemia	Asp/Asp	69	8	1 (Reference)		
	Asp/Glu	20	6	2.58	0.80-8.33	0.111
	Glu/Glu	1	0	2.72	0.10-72.35	0.548
	Asp/Glu+Glu/Glu	21	6	2.46	0.76-7.90	0.129
Neutropenia	Asp/Asp	73	7	1 (Reference)		
	Asp/Glu	18	5	2.89	0.82-10.19	0.097
	Glu/Glu	1	0	3.26	0.12-87.48	0.48
	Asp/Glu+Glu/Glu	19	5	2.74	0.78-9.61	0.114
Febrile neutropenia	Asp/Asp	71	6	1 (Reference)		
	Asp/Glu	20	6	3.55	1.03-12.21	0.044*
	Glu/Glu	1	0	3.66	0.13-99.39	0.44
	Asp/Glu+Glu/Glu	21	6	3.38	0.98-11.58	0.052
Mucositis	Asp/Asp	74	3	1 (Reference)		
	Asp/Glu	23	3	3.21	0.60-17.04	0.169
	Glu/Glu	1	0	7.09	0.24-207.43	0.255
	Asp/Glu+Glu/Glu	24	3	3.08	0.58-16.30	0.185
CINV	Asp/Asp	62	16	1 (Reference)		
	Asp/Glu	12	13	4.19	1.61-10.94	0.003*
	Glu/Glu	1	0	1.26	0.04-32.44	0.888
	Asp/Glu+Glu/Glu	13	13	3.87	1.50-9.96	0.005*
Fatigue	Asp/Asp	58	21	1 (Reference)		
	Asp/Glu	16	8	1.38	0.51-3.69	0.52
	Glu/Glu	1	0	0.9	0.03-23.12	0.952
	Asp/Glu+Glu/Glu	17	8	1.29	0.48-3.45	0.599
Bodyache	Asp/Asp	41	35	1 (Reference)		
	Asp/Glu	14	13	1.08	0.45-2.62	0.851
	Glu/Glu	1	0	0.38	0.01-6.86)	0.567
	Asp/Glu+Glu/Glu	15	13	1.01	0.42-2.42	0.972
Peripheral neuropathy	Asp/Asp	54	23	1 (Reference)		
	Asp/Glu	15	11	1.72	0.68-4.31	0.246
	Glu/Glu	1	0	0.77	0.03-19.67	0.876
	Asp/Glu+Glu/Glu	16	11	1.61	0.64-4.00	0.302

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

280, and the incidence of paclitaxel-induced toxicities in this patient cohort. Moreover, the hOGG1 (Ser326Cys) polymorphisms similarly exhibited no discernible association with the adverse toxicity responses to paclitaxel chemotherapy in BC patients.

In conclusion, the results of this study underscore a significant correlation between the XRCC3 (Ser241Cys) polymorphism and the occurrence of peripheral neuropathy induced by paclitaxel and doxorubicin chemotherapy in BC patients from the studied population. Additionally, the APE1 polymorphic variant 148Glu genotype exhibited a strong association with febrile neutropenia and chemotherapy-induced nausea and vomiting (CINV) following paclitaxel treatment. To the best of our knowledge, this is the first investigation of its kind to elucidate the relationship between *XRCC3* and *APE1* gene polymorphisms and chemotherapy-related toxicities in BC patients subjected to paclitaxel and doxorubicin therapy. These findings may serve as a foundational reference for future studies aiming to establish clinical correlations between various therapeutic modalities and their toxicological impacts in BC treatment.

Author Contribution Statement

Authors Contribution: Concept: KDD, RAG, SJB Design: KDD, RAG, Experimental Studies: PNR, SRK Clinical studies: RAG, AKG, Data analysis: KDD, RAG, Statistical analysis: KDD, Manuscript preparation: KDD, RAG, SJB All authors read and approved the final

Table 7. Effect of Genetic Polymorphisms of DNA Repair Gene (*hOGG1, cd-326, exon-7*) on Risk of Paclitaxel Chemotherapy Induced Hematological and Non-Hematological Toxicity Reactions in Breast Cancer Patients

Toxicities	hOGG1 Genotypes	Toxicity Grade ≤1	Toxicity Grade >1	OR	(95% CI)	pvalue
Anemia	Ser/Ser	37	5	1 (Reference)		
	Ser/Cys	38	7	1.326	0.39-4.68	0.622
	Cys/Cys	15	2	0.98	0.17-5.65	0.988
	Ser/Cys+Cys/Cys	53	9	1.25	0.38-4.05	0.702
Neutropenia	Ser/Ser	38	6	1 (Reference)		
	Ser/Cys	39	4	0.64	0.16-2.48	0.528
	Cys/Cys	14	3	1.35	0.29-6.17	0.692
	Ser/Cys+Cys/Cys	53	7	0.83	0.26-2.68	0.764
Febrile neutropenia	Ser/Ser	39	3	1 (Reference)		
	Ser/Cys	39	6	2	0.46-8.57	0.35
	Cys/Cys	14	3	2.78	0.50-15.44	0.241
	Ser/Cys+Cys/Cys	53	9	2.2	0.56-8.69	0.257
Mucositis	Ser/Ser	41	2	1 (Reference)		
	Ser/Cys	41	3	1.5	0.23-9.45	0.666
	Cys/Cys	16	1	1.28	0.10-15.13	0.844
	Ser/Cys+Cys/Cys	57	4	1.43	0.25-8.23	0.682
CINV	Ser/Ser	31	11	1 (Reference)		
	Ser/Cys	32	13	1.14	0.44-2.93	0.778
	Cys/Cys	12	5	1.17	0.33-4.09	0.801
	Ser/Cys+Cys/Cys	44	18	1.15	0.47-2.77	0.751
Fatigue	Ser/Ser	30	12	1 (Reference)		
	Ser/Cys	32	13	1.01	0.40-2.57	0.973
	Cys/Cys	13	4	0.76	0.20-2.83	0.693
	Ser/Cys+Cys/Cys	45	17	0.94	0.39-2.25	0.897
Bodyache	Ser/Ser	22	20	1 (Reference)		
	Ser/Cys	22	22	1.1	0.47-2.56	0.825
	Cys/Cys	12	6	0.55	0.17-1.74	0.309
	Ser/Cys+Cys/Cys	34	28	0.9	0.41-1.98	0.805
Peripheral neuropathy	Ser/Ser	29	11	1 (Reference)		
	Ser/Cys	27	18	1.75	0.70-4.38	0.227
	Cys/Cys	14	5	0.94	0.27-3.23	0.923
	Ser/Cys+Cys/Cys	41	23	1.47	0.62-3.50	0.373

OR, Odds ratio; CI, Confidence interval; p value determined based on $\chi 2$; Level of significance ($p< 0.05$)

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

Ethics Committee Approval

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

Abbreviations

APE1: Apurinic/apyrimidinic endonuclease 1
BC: Breast Cancer
BER:Base excision repair
BMI: Body Mass Index
CI: Confidence Interval
CINV: Chemotherapy Induced Nausea and Vomiting
DNA: Deoxyribose Nucleic Acid
ECOG: Estern Cooperative Oncology Group
EDTA: Ethylenediamdie Tetra acetate
ER: Estrogen Receptor
Her2: Humen Epidermal Growth Factor Receptor
hOGG1: Human 8-oxoguanine DNA N-Glycosylase 1

NCI-CTC: National Cancer Institute-Common Toxicity Criteria

NSCLC: Non-small cell lung carcinoma

PCR-RFLP: Polymerase Chain Reaction-Restriction Fragment Length Polymorphism

PR: Progesterone receptor

OR: Odds Ratio

SNP: Single nucleotide Polymorphism

XRCC: X ray repair cross complementing group

μl: Microliter

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.

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