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ORIGINAL RESEARCH

Polymorphism of *CYP3A4* and *ABCB1* genes increase the risk of neuropathy in breast cancer patients treated with paclitaxel and docetaxel

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Background: Interindividual variability of pharmacogenetics may account for unpredictable neurotoxicities of taxanes.

Methods: From March 2011 to June 2015, female patients with operable breast cancer who had received docetaxel- or paclitaxel-containing adjuvant chemotherapy were included in this study. All patients were treated with single-agent paclitaxel intravenously (IV) 175 mg/m^2 every 3 weeks for four cycles, or IV 80 mg/m^2 weekly for 12 cycles, and IV 100 mg/m^2 docetaxel for four cycles as adjuvant treatment. We evaluated the relationship between neurotoxicity of taxanes and single-nucleotide polymorphisms of *ABCB1*, *CYP3A4*, *ERCC1*, *ERCC2*, *FGFR4*, *TP53*, *ERBB2*, and *CYP2C8* genes. Taxane-induced neurotoxicity during the treatment was evaluated according to the National Cancer Institute Common Toxicity Criteria version 4.03 prior to each cycle. Chi-squared tests were used to compare the two groups, and multivariate binary logistic regression models were used for determining possible risk factors of neuropathy.

Results: Pharmacogenetic analysis was performed in 219 females. ABCB1 3435 TT genotype had significantly higher risk for grade ≥2 neurotoxicity (odds ratio [OR]: 2.759, 95% confidence interval [CI]: 1.172–6.493, *P*: 0.017) compared to TC and CC genotype, and also CYP3A4 392 AA and AG genotype had significantly higher risk for grade ≥2 neurotoxicity (OR: 2.259, 95% CI: 1.033–4.941, *P*: 0.038) compared to GG genotype. For *FDGF4* gene with AG and GG genotype, OR was 1.879 (95% CI: 1.001–3.525, *P*: 0.048) compared to AA genotype with regard to any grade of neuropathy risk. We could not find any other association of other genotypes with neurotoxicity grades.

Conclusion: *ABCB1* 3435 TT genotype and *CYP3A4* 392 AA/AG genotypes may be used as predictors of neurotoxicity during taxane chemotherapy.

Keywords: neurotoxicity, docetaxel, paclitaxel, CYP3A4, ABCB1, single nucleotide polymorphisms

Introduction

Influence of pharmacogenetic polymorphisms on drug pharmacokinetics and pharmacodynamics has been assessed in a large number of studies.[1–3] Interindividual variability in drug efficacy via metabolism and excretion could result in unpredictable treatment responses and toxicity. The potential effect of interindividual variability on these clinical variables was also conducted in several studies.[4,5]

Taxanes are one of the most active agents in the adjuvant and metastatic treatment of breast cancer. However, variability in toxicity and response remains a major problem for patients receiving taxanes. Significant variability of about four- to tenfold in paclitaxel clearance may contribute to the different clinical outcomes.[3]

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The cellular toxicity and activity of taxanes are likely controlled by multiple genes. Genes involved in transport through hepatobiliary and intestinal secretion of the parent drug by the adenosine triphosphate-binding cassette (ABC) genes, ABCB1, ABCC1, and ABCC2 isoforms; metabolism by the cytochrome P450 (CYP), CYP2C8, CYP3A4, and CYP3A5 isoforms; and pharmacodynamics by TP53 and CDKN1A genes, all appear to play a role in taxane efficacy and toxicity. In addition, DNA damage repair genes (eg, *ERCC1-2* [excision repair cross complementation]) may contribute to this process.[6–8]

The metabolism of taxanes consists of a CYP3A-mediated oxidation; docetaxel is predominantly metabolized by CYP3A4/5, whereas paclitaxel is metabolized by CYP2C8/CYP3A4 to inactive hydroxylated metabolites.[9,10] Elimination pathway of taxanes is mediated by the membrane-localized, energy-dependent drug efflux ABC transporter, P-glycoprotein (P-gp), which has been described in several polymorphisms.[11] The percentage of tumors expressing P-gp in breast cancer was 41.2%, and its expression rate increases after chemotherapy, which could result in failure of treatment.[12] It was reported that there is a possible relationship between single-nucleotide polymorphisms (SNPs) of the *ABCB1* gene, which affect the activity of P-gp, and the clinical outcome and toxicity of patients who were treated with taxane.[13,14]

Toxicities of taxanes, such as neuropathy, neutropenia, infusion-related reactions, and mucositis, causing interruption, dose reduction, or treatment modification, were evaluated for possible relationship with pharmacogenetic polymorphisms in some studies.[15,16] Taxane-induced neurotoxicity is mostly presented as a sensorial component, especially at the cumulative doses of drugs that breast cancer patients receive in the adjuvant setting. Accordingly, we evaluated whether ABCB1 3435C>T, CYP3A4 392A>G, ERCC1 60312 A>G, ERCC2 2251 A>C, fibroblast growth factor receptor 4 (FGFR4) 176520243 G>A, TP53 7579472 G>C, ERBB2 1873 A>G, and CYP2C8 35707 G>A polymorphisms have any effect on neuropathy risk in breast cancer patients treated with taxane in adjuvant setting.

Patients and methods

Study design

This retrospective study was conducted in Gaziantep University Oncology Hospital in Turkey. The study and written informed consent documentation were reviewed and approved by the Independent Ethics Committee of Gaziantep University, Medical Faculty. This study was conducted in compliance with the ethical principles according to the Declaration of Helsinki. The trial was designed to assess whether pharmacogenetic differences influence taxane-induced neurotoxicity.

Patient selection and genotypes

In total, 219 female breast cancer patients who underwent operation and received adjuvant taxane chemotherapy were enrolled, and pharmacogenetic analysis was carried out using the peripheral blood sample. Five-milliliter blood samples were collected in sterile-siliconized vacuum tubes with 2 mg/mL disodium EDTA. Immediately, genomic DNA was extracted from whole blood. Genetic variants of rs1045642 at chromosome (chr)7: 87138645 in ABCB1: C3435T minor allele frequency (MAF): A=0.3952/1,979, rs2740574 at chr7: 99784473 in CYP3A4: 392A>G (CYP3A4*1B) MAF: C=0.2308/1,156, rs3212935 at chr19: 45926775 in ERCC1: 60312A>G MAF: C=0.1026/514, rs13181 at chr19: 45854919 in ERCC2: 2251A>C MAF: G=0.2366/1,185, rs351855 at chr5: 176520243 in FGFR4: 176520243G>A MAF: A=0.2995/1,500, rs1042522 at chr17: 7579472 in TP53: 7579472G>C MAF: G=0.4571/2,289, rs1136201 at chr17: 37879588 in ERBB2: 1873A>G MAF: G=0.1214/608, rs1934951 at chr10: 96798548 in CYP2C8: 35707G>A MAF: T=0.2997/1,501 were studied by genotyping using the Fluidigm Digital Array (Fluidigm, South San Francisco, CA, USA). These polymorphisms were evaluated by using genomic DNA a 96.96 dynamic array on the BioMark HD System (Fluidigm). Dose, schedule, and duration of chemotherapy were noted. All patients had a diagnosis of breast carcinoma and were treated with single-agent paclitaxel intravenously (IV) 175 mg/m^2 per 3 weeks for four cycles, or IV 80 mg/m^2 weekly for 12 cycles, and IV 100 mg/m^2 docetaxel for four cycles. Some patients received additional biologic treatment concurrent with the taxane, such as the Her-2-targeted therapy for the subset of Her-2-overexpressing tumors. Patients without diabetes mellitus (DM) and patients with duration of DM <5 years were evaluated as low-risk patients for neuropathy. Duration of DM >5 years and age ≥65 years were evaluated as risk factors for neurotoxicity and were separately analyzed. Patients were divided into two groups: patients with neurotoxicity and those without. Grade <2 neurotoxicity and grade ≥2 neurotoxicity were also separately assessed.

Inclusion criteria were as follows: patients >18 years of age, both sexes, Eastern Cooperative Oncology Group performance status of 0–1, histologically proven breast cancer, and receiving paclitaxel or docetaxel regimen.

Exclusion criteria were as follows: patients with brain or leptomeningeal metastasis, previous platinum-based

or neurotoxic chemotherapy, history of alcohol dependency or concurrent use of other drugs known to influence serotonin levels, DM with preexisting neuropathy, unstable psychological conditions, use of antiepileptics, antidepressants, or lithium, and use of opioids (concomitant use of selected analgesics like nonsteroidal anti-inflammatory drugs was allowed).

Assessment of neurotoxicity

Diagnosis of taxane-induced peripheral neurotoxicity was evaluated based on symptom history, loss of deep tendon reflexes, and the presence of symmetrical "stocking-glove" numbness and burning–tingling after chemotherapy. Baseline taxane-induced peripheral neurotoxicity was assessed according to the National Cancer Institute Common Toxicity Criteria for Adverse Events version 4.03 grading scale (0= normal, 1= asymptomatic, weakness on physical examination, loss of reflexes, or paresthesias not interfering with daily function, 2= weakness and sensory alterations interfering with daily function, 3= weakness and sensory alterations interfering with activities of daily living or requiring bracing or assistive devices, and 4= life threatening, paralysis, disabling). Pretreatment evaluation for the patients who developed acute neurotoxicity was based on the ten-question form of the Neuropathic Pain Symptom Inventory and National Cancer Institute Common Toxicity Criteria for Adverse Events v 4.03 prior to each cycle of chemotherapy. Questions related to burning, squeezing, pressure, electric shocks, stabbing, evoked by brushing, evoked by pressure, pins and needles, and tingling were asked.

Statistical analysis

First, univariate analyses were performed to compare the two groups: chi-squared tests were used for categorical variables and univariate binary logistic regression method was used for estimating odds ratios (ORs) and 95% confidence interval (CI). Second, multivariate binary logistic regression models were used for adjusting confounding factors while determining possible risk factors. Multicollinearity was checked by calculating variance inflation factors. All univariate analyses were performed using SPSS for Windows, version 22.0 (IBM Corporation, Armonk, NY, USA). A two-sided *P*-value <0.05 was considered statistically significant.

Posterior power analysis was performed based on significant effects of *CYP3A4* and *ABCB1* genes on grade ≥ 2 neuropathy. Posterior power values were found to be 65% for CYP3A4 (effect size: 0.22 vs 0.10) and 48% for ABCB1 (effect size: 0.32 vs 0.15), when Type I error rate was 0.05.

Results

Two-hundred and nineteen breast cancer patients who were operated on and received adjuvant taxane chemotherapy were enrolled in this study. Of these patients, 55 (25.1%), 129 (58.9%, and 35 (15.9%) patients received weekly paclitaxel, docetaxel for 3 weeks, and paclitaxel for 3 weeks, respectively. Fifty one (23.3%) patients had DM. Approximately 116 (53%) patients experienced neurotoxicity. Sixty-four (62.1%) of these patients had Grade 1, 33 (32%) had Grade 2, and six (5.8%) patients had Grade 3 neurotoxicity. Two-hundred and eight patients were under the age of 65 years and eleven patients were over the age of 65 years. Neurotoxicity development and grading are summarized in Table 1 regarding age, status of DM, and receiving taxane chemotherapy type. Distribution of genetic polymorphism according to risk factors is listed in Table 2. Patient characteristics are summarized in Table 3.

According to pharmacogenotype

Genotypes of all genes and frequencies of variance according to age, duration of DM, and type of taxane chemotherapy are

Table 1 Neuropathy risks of patients according to DM status, type of drug, and age

Variables	N (%)	Neuropathy have/none (n)	*P*-value	OR (95% CI)	Neuropathy ≥ grade 2 have/none (n)	*P*-value	OR (95% CI)
DM status							
No DM and DM <5 years	199 (90.9)	90/109	0.091	0.44 (0.17–1.16)	30/169	0.001	4.6 (1.76–12.07)
DM ≥5 years	20 (9.1)	13/7		1	9/11		1
Taxane type							
Paclitaxel[a]	55 (25.1)	29/26	0.618		10/45		
Docetaxel	129 (58.9)	58/71			22/107	0.918	
Paclitaxel[b]	35 (16)	16/19			7/28		
Age, years							
<65	208 (95)	97/111	0.608	0.72 (0.21–2.46)	170/38	0.438	0.44 (0.056–3.60)
≥65	11 (5)	6/5		1	10/1		1

Notes: [a]Weekly, [b]thrice weekly.
Abbreviations: OR, odds ratio; DM, diabetes mellitus; CI, confidence interval; N, number of patients.

Table 2 Distribution of genetic polymorphism according to risk factors

Gene	SNP	Genotype	N (%)	Received paclitaxel vs docetaxel *P*-value	Age <65 vs ≥65 (years) *P*-value	No DM and DM <5 years vs DM ≥5 years *P*-value
CYP3A4	rs2740574	GG	92 (42.0)	0.643	0.619	0.555
		AG	11 (5.0)			
		AA	114 (52.1)			
CYP2C8[a]	rs1934951	AA	5 (5.6)	0.984	0.633	0.922
		AG	11 (12.4)			
		GG	73 (82)			
ABCB1	rs1045642	CC	30 (13.7)	0.421	0.208	0.876
		CT	159 (72.6)			
		TT	30 (13.7)			
ERCC1	rs3212935	AA	195 (89)	0.119	0.689	0.968
		AG	9 (4.1)			
		GG	12 (5.5)			
ERCC2	rs13181	AA	43 (19.6)	0.572	0.734	0.090
		AC	122 (55.7)			
		CC	25 (11.4)			
ERBB2	rs1136201	AA	192 (89.7)	0.44	0.283	0.848
		AG	15 (7.0)			
		GG	7 (3.3)			
P53	rs1042522	CC	27 (12.3)	0.344	0.666	0.885
		GC	41 (18.7)			
		GG	138 (63.0)			
FDGFR	rs351855	AA	53 (24.2)	0.132	0.856	0.505
		AG	49 (22.4)			
		GG	112 (51.1)			

Note: [a]It was studied only for patients who received paclitaxel.
Abbreviations: SNP, single-nucleotide polymorphism; DM, diabetes mellitus.

listed in Table 2 (for all groups $P>0.05$). OR of neuropathy risk and grade ≥2 neuropathy and risk according to gene SNPs are summarized in Table 4.

CYP3A4 genes were divided into two groups: GG genotype vs AA/AG genotypes. OR for any grade neuropathy was 0.64 (95% CI: 0.37–1.10, *P*: 0.109), and OR for > Grade 1 neuropathy was 2.26 (95% CI: 1.03–4.94, *P*: 0.038) in favor of AA/AG genotype.

Table 3 Patients' characteristics

Characteristic	N (%)
Age, years	
Median (min–max)	49.1 (21–79)
Pathology	
Invasive ductal carcinoma	146 (66.6)
Invasive lobular carcinoma	24 (10.9)
Other	49 (22.3)
Stage	
I	28 (13)
II	136 (62)
III	83 (25)
Menopause	
Premenopause	98 (45)
Postmenopause	121 (55)
Previous treatment	
FEC/FAC[a]	76 (35)
AC/EC[b]	143 (65)

Notes: [a]FEC: 5-fluorouracil 600 mg/m^2, epirubicin 100 mg/m^2, and cyclophosphamide 600 mg/m^2, every 21 days/FAC: 5-fluorouracil 500 mg/m^2, doxorubicin 50 mg/m^2, and cyclophosphamide 500 mg/m^2, every 21 days. [b]AC: cyclophosphamide 600 mg/m^2, doxorubicin 60 mg/m^2 every 21 days/EC: cyclophosphamide 600 mg/m^2, epirubicin 90 mg/m^2 every 21 days.

CYP2C8 genes were divided into two groups: GG genotype vs AA and AG genotypes. It was evaluated only for the paclitaxel group. OR for any grade neuropathy was 0.97 (95% CI: 0.33–2.87, *P*: 0.960), and OR for > Grade 1 neuropathy was 0.65 (95% CI: 0.18–2.34, *P*: 0.507).

ABCB1 genes were divided into two groups: CC/CT vs TT genotypes. OR for any grade neuropathy was 0.64 (95% CI: 0.29–1.39, *P*: 0.255), and OR for > Grade 1 neuropathy was 2.76 (95% CI: 1.17–6.49, *P*: 0.017) in favor of TT genotype.

ERCC1 genes were divided into two groups: AA vs AG and GG genotype. OR for any grade neuropathy was 0.96 (95% CI: 0.39–2.37, *P*: 0.934), and OR for > Grade 1 neuropathy was 1.15 (95% CI: 0.365–3.654, *P*: 0.806).

ERCC2 genes were divided into two groups: AA vs AC and CC genotypes. OR for any grade neuropathy was 1.01 (95% CI: 0.51–1.99, *P*: 0.977), and OR for > Grade 1 neuropathy was 0.55 (95% CI: 0.24–1.28, *P*: 0.161).

ERBB2 genes were divided into two groups: AA vs AG and GG genotypes. OR for any grade neuropathy was

Table 4 ORs of neuropathy risk and grade ≥2 neuropathy risk according to genotypes

Gene	Genotype	N	Neuropathy risk		Grade ≥2 neuropathy risk	
			OR (95% CI)	Significance	OR (95% CI)	Significance
CYP3A4	GG vs	217	1		1	
	AA and AG		0.641 (0.37–1.10)	0.109	2.259 (1.03–4.94)	0.038
CYP2C8	AA and AG vs	89	1	0.960	1	
	GG		0.973 (0.33–2.87)		0.650 (0.18–2.34)	0.507
ABCB1	CC and CT vs	219	1	0.255	1	
	TT		0.638 (0.29–1.39)		2.759 (1.17–6.49)	0.017
ERCC1	AA vs	216	1	0.934	1	
	AG and GG		0.962 (0.39–2.37)		1.1555 (0.36–3.65)	0.806
ERCC2	AA vs	190	1	0.977	1	
	AC and CC		1.010 (0.511–1.99)		0.550 (0.24–1.28)	0.161
ERBB2	AA vs	214	1	0.710	1	
	AG and GG		0.846 (0.35–2.04)		1.528 (0.52–4.45)	0.437
P53	CC vs	206	1	0.244	1	
	GC and GG		1.619 (0.72–3.65)		0.705 (0.26–1.89)	0.486
FDGFR	AA vs	214	1	0.048	1	
	AG and GG		1.879 (1.00–3.52)		0.628 (0.29–1.36)	0.234

Notes: A two-sided *P*-value <0.05 was considered statistically significant. Chi-squared test was used.
Abbreviations: OR, odds ratio; CI, confidence interval.

0.85 (95% CI: 0.35–2.04, *P*: 0.710), and OR for > Grade 1 neuropathy was 1.53 (95% CI: 0.52–4.45, *P*: 0.437).

P53 genes were divided into two groups: CC vs CG and GG genotypes. OR for any grade neuropathy was 1.62 (95% CI: 0.72–3.65, *P*: 0.244), and OR for > Grade 1 neuropathy was 0.70 (95% CI: 0.26–1.89, *P*: 0.486).

FDGFR genes were divided into two groups: AA vs AG and GG genotypes. OR for any grade neuropathy was 1.88 (95% CI: 1.00–3.52, *P*: 0.048), and OR for > Grade 1 neuropathy was 0.63 (95% CI: 0.29–1.36, *P*: 0.234) in favor of AG/GG genotype.

According to multivariate analysis, after adjusting for status of DM, CYP3A4 had an OR of 4.64 (95% CI: 1.08–5.50, *P*: 0.001) for > Grade 1 neuropathy. The OR was 5.47 (95% CI: 1.17–6.94, *P*: 0.019) for ABCB1.

Discussion

Taxanes produce a symmetric, axonal, predominantly sensory distal neuropathy with less prominent motor involvement, and more than 50% of patients experience varied degree of sensory peripheral neuropathy during their course of taxane treatment, with approximately 5%–30% having Grade 3 or 4 toxicity.[17,18] Sensorial neuropathy typically manifests as tingling–burning, stabbing, and pins and needles in the distal extremities, leading to loss of sensation, which may progress to loss of function that can be irreversible if treatment is continued; thus, taxane therapy is often discontinued once the patient experiences neurotoxicity over Grade 2. Taxane-induced sensorial neuropathy is associated with dose per cycle, treatment schedule, duration of infusion, cumulative dose, comorbidity, age (<65 vs >65 years), prior or concomitant administration of platinum compounds or vinca alcaloids, preexisting peripheral neuropathy, paraneoplastic syndromes, duration of DM, alcohol abuse, and also pharmacogenetic polymorphisms on taxane pharmacokinetics.[19–23]

Despite the considerable clinical activity of taxanes in various cancer types, variability in toxicity, unpredictability of clinical outcomes, and different responses to the treatment remain major problems. Numerous pharmacogenetic studies focused on the contribution of genetic variations to these interindividual differences in the patients receiving taxane therapy. The goal of this study was to identify pharmacogenetic polymorphisms that may be predictive to sensory peripheral neuropathy in patients receiving taxanes in adjuvant setting. We showed that polymorphisms in the *CYP3A4* and *ABCB1* genes are able to predict taxane neurotoxicity.

SNPs in *CYP450* and *ABCB1* genes are primarily responsible for taxane metabolism, which probably has an effect on the varying response. Although the relationship between pharmacogenetic variations of these polymorphisms and recurrence risk of early-stage breast cancer did not emerge, longer progression-free survival in local-advanced and metastatic setting was indicated in some studies.[24,25] It was found that TT genotype of ABCB1 C3435T was correlated with reduced expression of P-gp; thus, it reduced cellular elimination and maintained higher plasma concentrations of drugs.[26] A study showed that the TT genotype of *ABCB1* 3435 was associated with a higher plasma concentration of docetaxel

and longer overall survival. However, this was statistically insignificant in patients treated in a neoadjuvant setting (hazard ratio [HR]: 0.69, 95% CI: 0.33–1.26, *P*: 0.126). In addition, *ABCB1* 3435TT genotype caused more frequent Grade 3–4 neutropenia, febrile neutropenia, and diarrhea.[27]

Studies performed on pharmacogenetic polymorphism on the individual differences of taxane neurotoxicity are still inconclusive and are not enough to create a general perception. SNPs in the *CYP2C8*3* gene (rs11572080 and rs10509681), which decreases paclitaxel metabolic activity, lead to increased drug exposure and are associated with potential increases in neuropathy risk.[28,29] Hertz et al[30] evaluated the reflection of the aforementioned gene to clinical outcomes and toxicity of 111 breast cancer patients. It was found that patients carrying the CYP2C8*3 allele obtained more clinically complete response with neoadjuvant paclitaxel (55% vs 23%; OR: 3.92, 95% CI: 1.46–10.48, corrected *P*: 0.046) but tended to have higher incidence of > Grade 2 neuropathy (22% vs 8%; OR: 3.13, 95% CI: 0.89–11.01, uncorrected *P*: 0.075). Reanalysis of this study revealed that neuropathy seemed to be similar in both European-American and African-American patient cohorts.[24,30] In addition, Leskela et al[31] designed a study that evaluated 13 relevant polymorphisms in genes encoding paclitaxel metabolizing enzymes (*CYP2C8*, *CYP3A4*, and *CYP3A5*) and transporters (organic anion transporting polypeptide [OATP] 1B1, OATP1B3, and P-gp) in 118 Spanish cancer patients treated with paclitaxel. It was observed that CYP2C8 haplotype C and CYP3A5*3 were associated with decreased neuropathy risk (HR [per allele]: 0.55, 95% CI: 0.34–0.89, *P*: 0.014 and HR: 0.51, 95% CI: 0.30–0.86; and *P*: 0.012, respectively) and only being homozygous for the CYP2C8*3 allele was associated with increased neuropathy risk (HR: 1.72, 95% CI: 1.05–2.82; and *P*: 0.032). CYP3A4 was not associated with neuropathy, unlike in our study.[31] In our study, 89 patients received paclitaxel chemotherapy, and there was no statistically significant relationship between the neurotoxicity and polymorphism of CYP2C8: 35707G. A with GG genotype (OR: 0.97, 95% CI: 0.33–2.87) for neurotoxicity compared to GA and AA genotype (*P*: 0.96) and it was 0.65 (95% CI: 0.18–2.34 when evaluated according to grade *P*: 0.507).

Bosó et al[32] assessed a panel with 47 SNPs in 20 genes involved in taxane pathways (including CYP1B1, CYP2C8, CYP3A4-5, ABCB1-2, TP53, and ERCC1-2) on 113 female breast cancer patients taking docetaxel and paclitaxel. It was shown that two SNPs in two genes were associated with docetaxel toxicity ($P \leq 0.01$) (CYP3A4: infusion-related reactions, ERCC1: mucositis) and three SNPs in two different genes were associated with paclitaxel toxicity (CYP2C8: anemia; ERCC1: neuropathy, $P \leq 0.01$). Unlike in our study, ABCB1 (rs1045642) and CYP3A4 (rs2740574) were assessed, but it was not found to be related with taxane neurotoxicity. In our study, we evaluated ERCC1: 60312A>G (rs3212935), but a relationship with neurotoxicity was not observed (OR: 1.15, 95% CI: 0.36–3.65, *P*: 0.806).

Graan et al[33] assessed the CYP3A4*22, CYP2C8*3, CYP2C8*4, and ABCB1 3435 C>T genes for neuropathy in 239 patients receiving paclitaxel for various cancer types. Accordingly, CYP3A4*22 carriers had increased risk of developing severe neurotoxicity during paclitaxel therapy (*P*: 0.043) in the exploratory cohort analysis, and CYP3A4*22 carriers were also at risk of developing Grade 3 neurotoxicity (OR: 19.1, *P*: 0.001), which was consistent with the results of our study.[33] Additionally, another study showed that overpresentation of defective CYP3A4 variants was associated with the high-grade paclitaxel-induced neuropathy in patients receiving paclitaxel.[34] With GG genotype of CYP3A4 gene, decreased docetaxel clearance was seen compared to AA and AG genotype.[32,35] In our study, OR was 2.26 (95% CI: 1.03–4.94, *P*: 0.038) for patients with AA and AG genotype of CYP3A4: 392A>G (CYP3A4*1B) gene: rs2740574 for grade ≥2 neuropathy; however, OR was 0.64 (95% CI: 0.37–1.10, *P*: 0.109) when it was evaluated with regard to the existing neuropathy.

It was shown that TT genotype of ABCB1 3435 was associated with a higher plasma concentration of docetaxel and longer overall survival (HR: 0.69, 95% CI: 0.33–1.26, *P*: 0.126) and more frequent side effects such as Grade 3–4 neutropenia, febrile neutropenia, and diarrhea when compared to patients with other genotypes.[36] In another study, among patients who received paclitaxel, patients with the ABCB1 3435 CT genotype showed a tendency toward shorter overall survival than patients with the CC genotype (13.6 vs 18.5 months, *P*: 0.06), but this association was not observed in the frequency of Grade 3–4 hematologic or nonhematologic toxicity with 3435C>T genotype.[37] In our study, grade ≥2 neurotoxicity was more frequent in patients with TT genotype compared to TC/CC genotype (OR: 2.76, 95% CI: 1.17–6.49, *P*: 0.017).

It was found that *FGFR4* gene, causing a transmembrane domain missense mutation (Gly388Arg), is associated with poor disease outcome in node-positive breast cancer, but it was not evaluated in relation to neurotoxicity.[38] In our study, for *FGFR4* gene with AG and GG genotype, an OR of 1.88 (95% CI: 1.00–3.52, *P*: 0.048) was observed, compared to

AA genotype, for any grade neuropathy risk. However, there was no statistically significant difference when evaluated according to grade. This is the first study analyzing the effects of *FGFR4* gene for neurotoxicity risk.

The major limitation of this study is the retrospective design, the differences in the dose of paclitaxel used, and docetaxel treatment and schedule. The highlight of this study is the relationship between *ABCB1* and *CYP3A4* genotype with grade of taxane-induced neurotoxicity. The varying results of the aforementioned studies regarding polymorphism may be due to the different ethnic backgrounds of selected patient groups. Breast cancer is an attractive area for study for clinicians, thanks to longer survival duration and considerable treatment response. Supportive care could be neglected because of overfocusing on the main treatment goal. However, adverse events of chemotherapy like neuropathy, especially grade ≥2, are serious problems for breast cancer patients having such a long-term survival. This study showed that *ABCB1* and *CYP3A4* could not predict Grade 1 neurotoxicity, which generally spontaneously recovers after chemotherapy; however, these genes can be used as a predictor of severe neurotoxicity, which has a permanent course and leads to a decreased quality of life, together with other risk factors such as DM duration before the decision of treatment.

Conclusion

ABCB1 3435 TT genotype and CYP3A4 392 AA and AG genotype may predict the risk of taxane-induced severe neurotoxicity.

Disclosure

The authors report no conflicts of interests in this work.

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