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Effect of cyp1a1, cyp1b1 and cyp2c gene polymorphisms on doxorubicin and paclitaxel

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Abstract:
The genes encoding metabolizing cytochrome P450 enzyme are studied for their importance in cancer susceptibility. Therefore, it is of interest to identify the correlation of CYP1A, CYP1B and CYP2C gene polymorphisms (G-PMP) on drug response (DG-RS) and toxicity reactions in Indian population. 200 breast cancer (BC) patients received Doxorubicin (DXR) and paclitaxel (PCX) chemotherapy (CTP). Further, CTP induced hematological (HEM) and none (N)-HEM toxicity (TC) reactions were recorded. We found that, the univariate logistic regression analysis showed negative association of CYP1B1 (4326 C>G) G-PMP with microsites (OR=0.14, 95% CI: 0.03-0.54; p=0.004) in BC patients treated with DXR. Thus, protective effect of CYP1B1-PMP with DXR and PCX based CTP induced N-HEM-TC and CYP2C9-PMP with PCX induced body ache and CYP1A1-PMP with peripheral neuropathy in breast cancer patients.

Keywords: Breast cancer, G-PMP, CYP1A1, CYP1B1, CYP2C, chemotherapy, toxicity

Background:
Systemic CTP is an important therapeutic approach for breast cancer (BC) management where combinations of chemotherapeutic drugs including anthracyclines, platinum and taxanes treatment schedule have been widely adopted in the standard therapeutics **[1-3].** A different study showed that, CTP drugs (DRG) are the most active class of cytotoxic agents for treatment of both early and advanced breast cancers **[4].** Among CTP-DRG, a combination of DXR & PCX is used as standard regimen against advanced BC **[4].** Studies have also concluded that, this CTP-DRG can kill malignant cells. They can cause deleterious effects of normal healthy cells and cause adverse TC reactions too. Almost all CTP agents can cause severe after effects (acute TC) in patients treated with CTP where HEM and N-HEM adverse reactions are prominent **[4-6].** Despite all the advances that have happened in the recent times, the outcome predictions of CTP pattern cannot be generalized for all patients. Both the treatment responses and TC experienced are varied and unpredictable in each patient **[7-10].** Therefore, it is important to understand pharmacokinetic susceptibility of each individual towards the efficacy& TC of CTP-DRG. The pharmacogenomics studies evidenced that functional G-PMP encoding drug metabolizing enzymes (MT-E) can influence therapeutic (TPT) efficiency and treatment outcomes of different of CTP-DRG which can lead to TPT failure and adverse TC effects **[11-13].**

Studies have also shown that, there have been more than 2000 PMP identified in CYP family genes which are reported to determine treatment response or TC as the variant genotypes of MT-E encoding genes can alter activity of drug MT-E which may lead to anomalous drug MT **[11**]. It has been also evident from earlier findings that the PMP of majority of CYP genes are associated with TPT failure and CTP induced severe TC reactions **[11, 14-15].** Some of the earlier studies provided an association of CYP1A1*2A, CYP1A1*2C, CYP1B1*3, and CYP1B1*4-PMP with platinum based CTP response in lung cancer **[16-17].** A study have showed that, the CYP1A1 (rs1048943) PMP was significantly associated CTP response towards platinum based CTP in cervical cancer (CC) **[18].** Furthermore, studies have shown that, PMP of CYP1B1 may also contribute to the treatment response and survival of various CC patients **[17, 19-21].** A study on BC showed that, there was an association of CYP1B1*3-PMP with microsites reactions in response to PCX based CTP **[22].** Similarly another studies showed association of G-PMP of CYP1B1 with higher grade cardio toxicities in ovarian cancer (OC) patients **[23, 24].** Studies also shown that, the CYP2C family genes including CYP2C8, CYP2C9, play an important role in MT of commonly used anticancer drugs **[25-27].** Another study showed that, PMP variants of CYP2C8*2, CYP2C8*3, CYP2C9*2, CYP2C9*3 genes showed there was a negative association with TPT response towards neo-adjuvant CTP in BC patients **[8].**

Other studies also showed that, there was a significant association of CYP2C9-PMP in MT the TPT outcomes of CTP-DRG in head & neck squamous cell carcinoma (SQ-CC) **[28, 29].** Studies have also concluded that, PMP of CYP2C8*3 significantly induce HEM-TC such as neutropenia in OC patients (P) in response to platinum and taxane (PL-TX) based CTP **[30-32].** The CYP2C9 (rs1057910) PMP showed significant contribution in reduced response towards PL-TX based CTP-DRG in OCP **[33].** Conversely other studies showed non-significant impact of CYP1A1*2C, CYP1B1*4, CYP2D6*1A, CYP2E1*6, CYP2E1*7B PMP with either PL-TX based CTP response in in non-small cell lung carcinoma patients (CLC-P) **[15, 17, 34].** Similarly, another study has shown that, there was no significant association of CYP1A1-PMP was observed in response to CTP-DRG-TC reactions & overall survival of acute lymphoblastic leukemia patients (LP-LK-P) **[35].** Additionally, no association of CYP1A1 (rs4646903, rs1048943) PMP was noted with PL based CTP response in CC-P treated with cisplatin (CSP) **[36].** The literature studies showed that, the PMP of CYP1B1 showed no association with TPT response, outcomes and CTP-TC in OC-P **[23, 37].** Some other cohort studies showed non-significant correlation of CYP2C8 and CYP2C9 G-PMP with PCX plus CSP based CTP outcomes& CPT induced TC in OC-P **[23].** Therefore, it is of interest to assess the correlation of CYP1A1, CYP1B1, CYP2C genotypes with treatment efficacy & clinical outcomes in BC patients administered with DXR and PCX based CTP.

Materials and Methods:
The current study included 200 patients in the Department of Oncology, KHMRC. A detailed clinic-pathological (CL-PATH) &

demographic (DMOG) features along with follow up data of the patients were recorded. Of these patients, 104 patients were treated primarily with DXR followed by PCX & 96 patients were 1st treated with PCX thereafter DXR. The C-TPT effects were determined after every CTP cycle through blood testing (BD-TT). Patients were administered 4 cycles of combination CTP with DXR and Cyclophosphamide (CL-SP-AM), followed by 4 cycles of 3 weekly PCX. After receiving 1st cycle of CTP in each schedule, patient was followed again between 10th to 14th days after CTP for assessing CTP related TC. The patients administered CTP and observed assessment of treatment response & acute TC evaluation. The CTP induced HEM and N-HEM- TC were recorded and classified according to NCI-CTC Criteria. 5ml of whole blood from each patient was collected in sterile EDTA containing vacationer 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) (HI Media Laboratories) following the manufacturer's instructions. The genotyping of CYP450 enzyme genes including CYP1A1*2A, CYP1B1*3, CYP2C8*2, CYP2C8*3, CYP2C9*2, CYP2C9*3, were performed PCR restriction fragment length polymorphisms (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 CYP450 genes are shown in **Table 1.**

Table 1: The list of candidate ABCB genes selected

Gene/ Genotype	RS number	Nucleotide change	Primer Sequence (Forward/Reverse)	PCR product	Digestion conditions	Dominant (Wild type)	Heterozygous	Recessive (Mutant)
CYP1A1	*rs1048943*	(A>G)	FP: 5′- AAA GGC TGG GTC CAC CCT CT -3′	322 bp	1 Unit of NcoI	250 bp	322 bp	322 bp
Ex-7 A4889G			RP: 5′- AAA GAC CTC CCA GCG GGC CA-3′		Incubation at 37˚C for 1h	72 bp	250 bp	
							72 bp	
CYP1B1	*rs1056836*	(C>G)	FP: 5′-TTG GCC CTG AAA TCG CAC CGG T-3′	240 bp	1 Unit of BseNI	194 bp	240 bp	240 bp
Ex-3			RP: 5′-CCA AGG ACA CTG TGG TTT TTG TCA AGC AG-3′		Incubation at 37˚C for 1h	46 bp	194 bp	
C4326G)							46 bp	
CYP2C8*2	*rs11572103*	(T>A)	FP: 5′-AAA GTA AAA GAA CAC CAA GC-3′	167 bp	1 Unit of Kzo9I	69 bp	NIL	98 bp
Ex5			RP: 5'-AAA CAT CCT TAG TAA ATT ACA-3′		Incubation at 37˚C for 1h	65 bp		69 bp
T805A						33 bp		
CYP2C8*3	*rs11572080*	(G>A)	FP: 5′- AGG CAA TTC CCC AAT ATC TC-3′	467 bp	1 Unit of BseRI	310 bp	NIL	356 bp
Ex3			RP: 5′-CAG GAT GCG CAA TGA AGA C-3′		Incubation at 37˚C for 1h	111 bp		111 bp
G416A						46 bp		
CYP2C9*2	*rs1799853*	(C>T)	FP: 5'-CAC TGG CTG AAA GAG CTA ACA GAG-3'	372 bp	1 Unit of AspS9I	179 bp	NIL	253 bp
Ex-3			RP: 5'-GTG ATA TGG AGT AGG GTC ACC CAC-3'		Incubation at 37˚C for 1h	119 bp		119 bp
C430T						74 bp		
CYP2C9*3	*rs1057910*	(A>C)	FP:5'-AGG AAG AGA TTG AAC GTG TGA-3'	130 bp	1 Unit of ErhI	104 bp	NIL	130 bp
Ex-7 A1075C			RP: 5'GGC AGG CTG GTG GGG AGA AGG CCA A-3'		Incubation at 37˚C for 1h	26 bp		

Inclusion criteria:
[1] Histopathology confirm report
[2] Diagnosed with BC & planned for standard CTP (DXR & PCX).

Exclusion criteria:
[1] Patients with no pathological diagnosis
[2] Incomplete treatment
[3] Incomplete follow-up
[4] Patients with other comorbidities
[5] Abnormal liver
[6] Renal function tests

Statistical analyses:
All tests were carried out using SPSS 11 Software. The relative risk, Odds Ratio (OR) & corresponding 95% confidence intervals (CI) were determined through unconditional multiple logistic regression (M-LR). The p values <0.05 were considered as statistically significant.

Table 2: Univariate analysis of candidate SNPS of cytochrome p450

		Anemia (AM)			
Gene Name	**Genotype**	**Grade ≤1**	**Grade >1**	**OR (95% CI)**	**p value**

SNP		(n=81)	(n=23)		
CYP1A1	A/A	38	9	1 (Reference)	
rs1048943	A/G+G/G	43	14	1.37 (0.53-3.53)	0.508
CYP1B1	C/C	44	13	1 (Reference)	
rs1056836	C/G+G/G	37	10	0.91 (0.35-2.32)	0.851
CYP2C8*2	T/T	77	23	1 (Reference)	
rs11572103	T/A+A/A	4	0	0.36 (0.01-7.05)	0.505
CYP2C8*3	G/G	55	14	1 (Reference)	
rs11572080	G/A+A+A	26	9	1.35 (0.52-3.54)	0.529
CYP2C9*2	C/C	74	23	1 (Reference)	
rs1799853	C/T+T/T	7	0	0.21 (0.01-3.84)	0.293
CYP2C9*3	A/A	66	18	1 (Reference)	
rs1057910	A/C+C/C	15	5	1.22 (0.39-3.81)	0.729
		Neutropenia(NP)			
		(n=79)	**(n=25)**		
CYP1A1	A/A	37	10	1 (Reference)	
rs1048943	A/G+G/G	42	15	1.32 (0.52-3.29)	0.55
CYP1B1	C/C	40	17	1 (Reference)	
rs1056836	C/G+G/G	39	8	0.48 (0.18-1.24)	0.132
CYP2C8*2	T/T	75	25	1 (Reference)	
rs11572103	T/A+A/A	4	0	0.32 (0.01-6.32)	0.461
CYP2C8*3	G/G	55	14	1 (Reference)	
rs11572080	G/A+A+A	24	11	1.80 (0.71-4.53)	0.212
CYP2C9*2	C/C	73	24	1 (Reference)	
rs1799853	C/T+T/T	6	1	0.50 (0.05-4.42)	0.538
CYP2C9*3	A/A	63	21	1 (Reference)	
rs1057910	A/C+C/C	16	4	0.75 (0.22-2.49)	0.639
		Febrile Neutropenia(FB-NP)			
		(n=80)	**(n=24)**		
CYP1A1	A/A	37	10	1 (Reference)	
rs1048943	A/G+G/G	43	14	1.20 (0.47-3.03)	0.692
CYP1B1	C/C	42	15	1 (Reference)	
rs1056836	C/G+G/G	38	9	0.66 (0.26-1.69)	0.389
CYP2C8*2	T/T	76	24	1 (Reference)	
rs11572103	T/A+A/A	4	0	0.34 (0.01-6.67)	0.482
CYP2C8*3	G/G	54	15	1 (Reference)	
rs11572080	G/A+A+A	26	9	1.24 (0.48-3.22)	0.649
CYP2C9*2	C/C	73	24	1 (Reference)	
rs1799853	C/T+T/T	7	0	0.20 (0.01-3.63)	0.276
CYP2C9*3	A/A	62	22	1 (Reference)	
rs1057910	A/C+C/C	18	2	0.31 (0.06-1.46)	0.139
		Thrombocytopenia(TMCP)			
		(n=97)	**(n=7)**		
CYP1A1	A/A	45	2	1 (reference)	
rs1048943	A/G+G/G	52	5	2.16 (0.40-11.69)	0.37
CYP1B1	C/C	53	4	1 (reference)	
rs1056836	C/G+G/G	44	3	0.90 (0.19-4.25)	0.897
CYP2C8*2	T/T	93	7	1 (reference)	
rs11572103	T/A+A/A	4	0	2.11 (0.09-47.48)	0.638
CYP2C8*3	G/G	66	3	1 (reference)	
rs11572080	G/A+A+A	31	4	2.83 (0.59-13.46)	0.188
CYP2C9*2	C/C	90	7	1 (reference)	
rs1799853	C/T+T/T	7	0	0.80 (0.04-15.49)	0.885
CYP2C9*3	A/A	78	6	1 (reference)	
rs1057910	A/C+C/C	19	1	0.68 (0.07-6.02)	0.732

Table 3: Risk of DXR-CTP induced severe TC of n-hem reactions in BC-p.

		Mucositis (MCO)			
Gene Name	**Genotype**	**Grade ≤1**	**Grade >1**	**OR (95% CI)**	**p value**
SNP		**(n=88)**	**(n=16)**		
CYP1A1	A/A	42	5	1 (Reference)	
rs1048943	A/G+G/G	46	11	2.00 (0.64-6.26)	0.229
CYP1B1	C/C	34	13	1 (Reference)	
rs1056836	C/G+G/G	54	3	0.14 (0.03-0.54)	0.004*
CYP2C8*2	T/T	84	16	1 (Reference)	
rs11572103	T/A+A/A	4	0	0.56 (0.02-11.08)	0.709
CYP2C8*3	G/G	59	10	1 (Reference)	
rs11572080	G/A+A+A	29	6	1.22 (0.40-3.68)	0.723
CYP2C9*2	C/C	78	16	1 (Reference)	
rs1799853	C/T+T/T	7	0	0.31 (0.01-5.83)	0.439
CYP2C9*3	A/A	69	15	1 (Reference)	
rs1057910	A/C+C/C	19	1	0.24 (0.03-1.95)	0.182

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		CINV			
		(n=70)	**(n=34)**		
CYP1A1	A/A	27	20	1 (Reference)	
rs1048943	A/G+G/G	43	14	0.43 (0.19-1.01)	0.053
CYP1B1	C/C	38	19	1 (Reference)	
rs1056836	C/G+G/G	32	15	0.93 (0.41-2.13)	0.787
CYP2C8*2	T/T	66	34	1 (Reference)	
rs11572103	T/A+A/A	4	0	0.21 (0.01-4.09)	0.306
CYP2C8*3	G/G	47	22	1 (Reference)	
rs11572080	G/A+A+A	23	12	1.11 (0.47-2.64)	0.805
CYP2C9*2	C/C	64	33	1 (Reference)	
rs1799853	C/T+T/T	6	1	0.32 (0.03-2.79)	0.305
CYP2C9*3	A/A	68	30	1 (Reference)	
rs1057910	A/C+C/C	16	4	0.56 (0.17-1.83)	0.344
		Fatigue(FTG)			
		(n=67)	**(n=37)**		
CYP1A1	A/A	31	16	1 (Reference)	
rs1048943	A/G+G/G	36	21	1.132 (0.50-2.53)	0.766
CYP1B1	C/C	35	22	1 (Reference)	
rs1056836	C/G+G/G	32	15	0.74 (0.33-1.68)	0.479
CYP2C8*2	T/T	64	36	1 (Reference)	
rs11572103	T/A+A/A	3	1	0.59 (0.05-5.90)	0.655
CYP2C8*3	G/G	45	24	1 (Reference)	
rs11572080	G/A+A+A	22	13	1.10 (0.47-2.58)	0.812
CYP2C9*2	C/C	60	37	1 (Reference)	
rs1799853	C/T+T/T	7	0	0.10 (0.006-1.93)	0.13
CYP2C9*3	A/A	56	28	1 (Reference)	
rs1057910	A/C+C/C	11	9	1.63 (0.60-4.40)	0.33
		Body ache(BAC)			
		(n=89)	**(n=15)**		
CYP1A1	A/A	39	8	1 (Reference)	
rs1048943	A/G+G/G	50	7	0.68 (0.22-2.04)	0.495
CYP1B1	C/C	46	11	1 (Reference)	
rs1056836	C/G+G/G	43	4	0.38 (0.11-1.31)	0.128
CYP2C8*2	T/T	86	14	1 (Reference)	
rs11572103	T/A+A/A	3	1	2.04 (0.19-21.10)	0.547
CYP2C8*3	G/G	60	9	1 (Reference)	
rs11572080	G/A+A+A	29	6	1.37 (0.44-4.24)	0.575
CYP2C9*2	C/C	82	15	1 (Reference)	
rs1799853	C/T+T/T	7	0	0.35 (0.01-6.53)	0.485
CYP2C9*3	A/A	71	13	1 (Reference)	
rs1057910	A/C+C/C	18	2	0.60 (0.12-2.93)	0.534
		Peripheral Neuropathy(PP-NP)			
		(n=99)	**(n=5)**		
CYP1A1	A/A	45	2	1 (Reference)	
rs1048943	A/G+G/G	54	3	1.25 (0.20-7.81)	0.811
CYP1B1	C/C	54	3	1 (Reference)	
rs1056836	C/G+G/G	45	2	0.80 (0.12-4.99)	0.811
CYP2C8*2	T/T	95	5	1 (Reference)	
rs11572103	T/A+A/A	4	0	1.92 (0.09-40.55)	0.672
CYP2C8*3	G/G	68	1	1 (Reference)	
rs11572080	G/A+A+A	31	4	8.77 (0.94-81.77)	0.056
CYP2C9*2	C/C	92	5	1 (Reference)	
rs1799853	C/T+T/T	7	0	1.12 (0.05-22.27)	0.94
CYP2C9*3	A/A	79	5	1 (Reference)	
rs1057910	A/C+C/C	20	0	0.35 (0.01-6.63)	0.486

Table 4: Association of CYP1A1, CYP1B1and CYP2C gene polymorphisms with demographic and clinic-pathological factors of BC patients

Characteristics	**CYP1A1 (rs1048943)**		**CYP1B1 (rs1056836)**		**CYP2C8*2 (rs11572103)**	
	A/A	**A/G+A/A**	**G/G**	**G/C+C/C**	**T/T**	**T/A+A/A**
	No (%)	**No (%)**	**No (%)**	**No (%)**	**No (%)**	**No (%)**
Age						
≤ 40	15 (7.50)	28 (14.00)	21 (10.50)	22 (11.00)	42 (21.00)	1 (0.50)
>40	81 (40.50)	76 (38.00)	79 (39.50)	78 (39.00)	148 (74.00)	9 (4.50)
OR (95% CI)	1 (Reference)	0.50 (0.24-1.01)	1 (Reference)	0.94 (0.47-1.85)	1 (Reference)	2.55 (0.31-20.73)
p value		0.054		0.863		0.38
BMI Kg/m2						
≤ 25	65 (32.50)	57 (28.50)	64 (32.00)	58 (29.00)	113 (56.50)	9 (4.50)
>25	31 (15.50)	47 (23.50)	36 (18.00)	42 (21.00)	77 (38.50)	1 (0.50)
OR (95% CI)	1 (Reference)	1.72 (0.97-3.07)	1 (Reference)	1.28 (0.72-2.27)	1 (Reference)	0.16 (0.02-1.31)
p value		0.062		0.384		0.088
Clinical TNM Grade						

≤ Stage II	52 (26.00)	50 (25.00)	55 (27.50)	47 (23.50)	101 (50.50)	1 (0.50)
> Stage II	44 (22.00)	54 (27.00)	45 (22.50)	53 (26.50)	89 (44.50)	9 (4.50)
OR (95% CI)	1 (Reference)	1.27 (0.73-2.22)	1 (Reference)	1.37 (0.79-2.40)	1 (Reference)	10.21 (1.26-82.21)
p value		0.389		0.258		0.029
Histopathological(H-PATH) TNM Grade						
≤ Stage II	39 (19.50)	51 (25.50)	38 (19.00)	52 (26.00)	89 (44.50)	1 (0.50)
> Stage II	57 (28.50)	53 (26.50)	62 (31.00)	48 (24.00)	101 (50.50)	9 (4.50)
OR (95% CI)	1 (Reference)	0.71 (0.40-1.24)	1 (Reference)	0.56 (0.32-0.99)	1 (Reference)	7.93 (0.98-63.83)
p value		0.232		**0.047***		0.051
Hormone Receptor Status(HR-S)						
ER/PR +ve	41 (20.50)	42 (21.00)	33 (16.50)	50 (25.00)	80 (40.00)	3 (1.50)
ER/PR -ve	55 (27.50)	62 (31.00)	67 (33.50)	50 (25.00)	110 (55.00)	7 (3.50)
OR (95% CI)	1 (Reference)	1.10 (0.62-1.93)	1 (Reference)	0.53 (0.29-0.94)	1 (Reference)	1.69 (0.42-6.76)
p value		0.739		**0.031***		0.453
Her2 +ve	20 (10.00)	12 (6.00)	17 (8.50)	15 (7.50)	31 (15.50)	1 (0.50)
Her2 -ve	76 (38.00)	92 (46.00)	83 (41.50)	85 (42.50)	159 79.50)	9 (4.50)
OR (95% CI)	1 (Reference)	2.01 (0.92-4.39)	1(Reference)	1.16 (0.54-2.47)	1 (Reference)	1.75 (0.21-14.35)
p value		0.076		0.699		0.6

Results:

Table 2 shows that, severe toxicity (grade >1) AM, 25 patients showed severe NP, 24 patients showed FB-NP & 7 patients faced TMCP. The severe N-HEM-TC with grade >1 were recorded as mucositis in 16 patients, CINV in 34 patients, fatigue in 37 patients, body ache in 15 patients and peripheral neuropathy in 5 patients after treatment with DXR-CTP. **Table 3** shows that, rs1056836 SNP of CYP1B1 showed negative association with protective effects in BC-P in response to MCO reactions (OR=0.14, 95% CI: 0.03-0.54; p=0.004). The ORs with 95% CI of other SNPs for their correlation with MCO were: (CYP1A1 (rs1048943) (OR=2.00, 95% CI: 0.64-06.26; p=0.0229), CYP2C8*2(rs11572103) (OR=0.56, 940-3.68; p=0.723), CYP2C9*2 (rs1799853) (OR=0.31, 95% CI: 0.01-5.83; p=0.439), CYP2C9*3 (rs1057910) (OR=0.24, 95% CI: 0.03-1.95; p=0.182). We noted no association of G-PMP of other CYP450 genes with CINV in BC-P. **Table 4** shows that, significant negative association of variant (G/C) genotype of CYP1B1 (rs1056836) with H-PATH TNM grade>II (OR=0.56, 95% CI: 0.32-0.99; p=0.047) whereas other genotypes of CYP1A1 and CYP2C genotypes showed no association with H-PATH confirmed TNM grade >II. None of the genotype of CYP1A1, CYP1B1, CYP2C showed association with clinically confirmed TNM grade >II of the BC-P. The results also showed that CYP1B1 (G>C) PMP showed significant negative association with ER/PR HR-S of BC patients (OR=0.53, 95% CI: 0.29-0.94; p=0.031) whereas the genotype distribution of other genotypes showed no association with ER/PR or Her2 hormone receptors respectively.

Discussion:

Several pharmacogenomics studies revealed that the patient's response towards different CTP-DRG is not similar because of diverse genetic susceptibility of each individual towards the treatment response **[11-13].** The pharmacogenomics studies evidenced that polymorphisms of CYP450 genes encoding CYP450 enzymes could influence therapeutic efficiency and treatment outcomes of different CTP-DRG **[7-10]**. Studies have also shown that, the CYP1A1 G-PMP was significantly studied for their association with C-TPT response towards PL & TX and based CTP in different forms of cancer **[16-18].**

When we studied the PMP of CYP1A1 (rs1048943) in response to CTP, we observed that CYP1A1 variant allele showed negative association with peripheral neuropathy in BC-P when treated with paclitaxel based CTP (OR=0.35, 95% CI: 0.15-0.84; p=0.019). Similarly, CYP1B1*3 PMP & its association with adryamycin & PCX based CTP noted negative association with protective effects of CYP1B1 (rs1056836) with MCO (OR=0.14, 95% CI: 0.03-0.54; p=0.004) in DXR based CTP & peripheral neuropathy in PCX based CTP in BC-P (OR=0.41, 95% CI: 0.17-0.96; p=0.040). These results are in contrast to the other studies reported a positive association of CYP1B1*3 PMP with CTP response and severe TC in BC & OC **[22-24].**

In contrast to these findings, other researchers depicted significant association of CYP2C8*3 with HEM-TC toxicity such as neutropenia in ovarian cancer patients in response to platinum and taxane based CTP **[30-32]**. The CYP2C9 (rs1057910) polymorphism showed significant contribution in reduced response towards platinum based C-TPT-DRG in OC-P **[33].** CYP2C9-PMP modulates TPT outcomes of chemotherapy drugs in head and neck SQ-CC **[28-29].** Similarly, no significant association of CYP1A1-PMP was observed in response to C-TPT-DRG-TC reactions & overall survival of acute LP-LK-P **[35].** No association of CYP1A1 (rs4646903, rs1048943) PMP was noted with PL based CTP response in CC-P treated with cisplatin [36]. The literature studies showed that the PMP of CYP1B1 showed no association with TPT response, outcomes & CPT chemotherapy toxicity in OC-P **[23, 37]**.

Some other cohort studies showed non-significant correlation of CYP2C8 and CYP2C9 G-PMP with PCX plus cisplatin based CTP outcomes & CTP induced TC in OC-P **[23]**. There is a strong link between CYP2C9*2 and both hematological and non-hematological side effects of Adriamycin-based chemotherapy in a certain group of breast cancer patients. It was found that the CYP2C19*2 polymorphic variant genotype was strongly linked to anemia, neutropenia, and thrombocytopenia after Adriamycin treatment. The CYP17 polymorphism was strongly linked to body pain and peripheral neuropathy in people who were

getting paclitaxel-based chemotherapy. So, they came to the conclusion that this is the first study of its kind to look at how chemotherapy based on Adriamycin affects metabolic gene polymorphisms in people with breast cancer **[38]**.

While CYP2C19*2 rs4244285 possessed a significantly decreased risk (OR: 0.53, 95% CI: 0.33-0.85 P 0.009) of CC in the studied rural population, the CYP1B1*3 rs1056836 (Leu4326Val) polymorphism showed a significantly raised risk (OR = 3.28; 95% CI: 2.18-4.94; P 0.0001).A study found that the rs10244285 SNP of CYP2C19*2 lowers the risk of cancer in the group that was looked at, while the rs1056836 SNP of CYP1B1*3 raises the risk of cancer **[39]**.

Conclusion:

Data shows negative association of CYP1B1 with DXR based CTP induced N-HEM-TC including MCO & PP-NP in PCX based CTP in BC patients of the selected population. Moreover, PMP of CYP2C8 and CYP2C9 showed no association with either of HEM or N-HEM-TC in response to selected CTP regime in BC patients. Furthermore longitudinal studies are recommended to validate the results of our study.

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