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Influence of *ABCB1* genetic polymorphisms on the antiemetic response to ondansetron-based medication for cisplatin-based chemotherapy in South Indian cancer patients in a tertiary care hospital

Ayyar Porkodi[1*], Deepak Gopal Shewade[2], Goud Alladi Charanraj[3]

[1] Pharmacology, SRM Medical College Hospital and Research Centre, SRM Institute of Science and Technology, Kattankulathur, India
[2] Pharmacology, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), India
[3] Department of Dermatology & STD, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), India

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ABSTRACT

Genetic variations in the receptor, metabolizing enzymes and transporters may explain a part of the variation in anti-emetic response to ondansetron among cancer patients. This study assesses the role of *ABCB1* genetic polymorphisms in the anti-emetic efficacy of ondansetron-based medication for cisplatin-based chemotherapy in South Indian cancer patients.

The frequencies of common *ABCB1* polymorphisms (rs1045642; *C>T*, rs1128503; *C>T* and rs2032582; *G>T/A*) were studied in 234 South Indian cancer patients receiving cisplatin-based chemotherapy. Comparison of nausea and vomiting with respect to number of episodes and severity by Visual Analogue Scale (VAS), and Common Terminology Criteria for Adverse Events version 4.0 (CTCAEv4.0) was made across genotype groups of each polymorphism.

TT genotype carriers of all three polymorphisms had significantly lesser incidence of nausea and vomiting when compared to other genotypes of the respective polymorphisms during 2-24 hours and on days 2-5. Median VAS score for nausea and vomiting was also lower for *TT* genotype carriers at each time point except for nausea on days 2-5 (p=0.057) of C*3435T*. As per CTCAEv4.0, *TT* genotype carriers had less severe grade at each time point except for days 2-5 nausea (p=0.278) and vomiting (p=0.219) of C3435T and nausea on days 2-5 (p=0.068) of G2677T/A: *TT* genotype of *ABCB1* genetic polymorphisms was associated with anti-emetic response to ondansetron-based medication in the population studied. Hence, genotyping for *ABCB1* polymorphisms may be used as a tool to predict response to ondansetron.

INTRODUCTION

Nausea and vomiting, ranked by cancer patients as the most distressing and unpleasant side effect of cancer chemotherapy, adversely affects the daily lives of cancer patients [1,2]. Chemotherapy-induced nausea and vomiting (CINV) can be classified into acute (within 24 hours), delayed (24-120 hours), anticipatory (prior to chemotherapy), breakthrough and refractory [3-5]. Delayed CINV, when compared to acute CINV, is more common and less treatment responsive [6]. CINV may cause dehydration, poor nutrition, wound gaping, esophageal tears and acid-base disorder (metabolic alkalosis). Psychological adverse effects such as depression, fatigue, and poor self-care may also result. Together, CINV culminates in poor quality of life and affects compliance to chemotherapeutic drugs causing discontinuation of potentially lifesaving cancer treatment [7,8]. Insight into the pathophysiology in the genesis of CINV, particularly the discovery of serotonin – 5-HT3 receptor interaction was a turning point in the management of CINV [9]. 5HT3 receptor antagonists prevent CINV by antagonizing 5HT3 receptors in the abdominal vagal afferents peripherally and the CTZ centrally [10]. The introduction of ondansetron, a first-in-class drug of 5-HT3 receptor antagonists, marked the dawn of a new era in the management of CINV [11,12].

* **Corresponding author**
e-mail: porkodia@srmist.edu.in

5-HT3 receptor antagonists form an integral component of anti-emetic regimen for prophylaxis of CINV caused by moderately and highly emetogenic chemotherapy as advised by notable professional oncology groups worldwide [13]. Still, CINV amelioration remains an unmet need for a significant proportion of cancer patients receiving chemotherapy. Ondansetron, a widely used 5-HT3 receptor antagonist, is metabolised by CYP450 enzymes, mainly CYP2D6, CYP3A4 and CYP1A2 and a substrate for P-glycoprotein, a membrane-bound ATP-dependent efflux protein coded by *ABCB1* (ATP-binding cassette transporter subfamily B member 1) gene [14].

To account for the varying anti-emetic response to ondansetron, studies have been conducted on the genetic variations in receptor subunits, drug metabolizing enzymes and transport proteins. Such studies yielded varying results. Among various *ABCB1* polymorphisms identified, three single nucleotide polymorphisms, namely, *C3435T*, *G2677T/A* and *C1236T*, have been found to occur with higher frequencies [15]. These polymorphisms can result in altered functioning of the efflux transporter and hence can cause variation in the bioavailability, distribution, and efficacy of ondansetron. Accordingly, studies have shown greater anti-emetic efficacy in patients with *3435TT* and *2677TT* genotypic variants of *ABCB1* gene [16-18].

The pharmacogenetics of ondansetron has not been studied in the Indian population. The *C3435T* and *G2677T* genetic polymorphisms of *ABCB1* have, however, been well documented in South Indian population [19]. Hence, we planned to study the role of ABCB1 genetic polymorphisms, namely, *C3435T*, *G2677T/A* and *C1236T*, in the anti-emetic efficacy of ondansetron-based medication for cisplatin-based chemotherapy in South Indian cancer patients.

MATERIALS AND METHODS

This prospective study was done at JIPMER, India in accordance with the ethical standards as laid down in the Declaration of Helsinki after approval by the Institute ethics committee for human studies. The study period was from October 2015 to March 2017.

Study participants

This study includes patients from outpatient department and inpatients receiving ondansetron-based medication for cisplatin-based chemotherapy. Patients of either gender belonging to the 18-65 years age group and are of South Indian origin (history of belonging to any of the south Indian states viz., Andhra Pradesh, Telangana, Karnataka, Kerala, Tamil Nadu, and Pondicherry, for the last three generations and speaking the native language as the mother tongue) receiving ondansetron-based medication for cisplatin-based chemotherapy were eligible for the study. Use of other anti-emetics such as benzodiazepines or neuroleptics, use of inducers or inhibitors of CYPP3A4 and CYP2D6, pregnancy, lactation, liver, or renal dysfunction were the exclusion criteria used. After genotyping, eligible patients of each Single Nucleotide Polymorphism (SNP) group were subdivided into three genotype groups:

- *ABCB1 C3435T*:
  - *CC* normal
  - *CT* heterozygous variant
  - *TT* homozygous variant
- *ABCB1 G2677T*/A:
  - *GG* normal
  - *GT* heterozygous variant
  - *GA* heterozygous variant
  - *TA* heterozygous variant
  - *TT* homozygous variant
  - *AA* homozygous variant
- *ABCB1 C1236T*:
  - *CC* normal
  - *CT* heterozygous variant
  - *TT* homozygous variant.

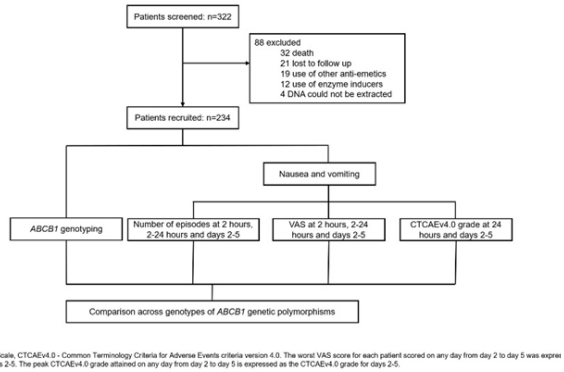
Sample size calculation

The sample size was calculated using PS Power and Sample Size Calculator Software Ver. 3.0. The α value was taken as 0.05, power as 85%, control to case ratio of 0.4 (based on genotype frequency) [19], P0 (probability of complete control of nausea and vomiting for normal variant CC of C3435T) as 0.5 and P1 (probability of complete control of nausea and vomiting for homozygous variant TT of C3435T) as 0.73 (data from the previous study on ABCB1 C3435T by Babaoglu *et al*.) [17]. The calculated sample size in each group was adjusted to genotype frequency.

Study procedure

The patients were screened for eligibility criteria, and they were recruited into the study after obtaining written informed consent. The details of patients regarding age, address, disease condition, anticancer medication details, antiemetic medication details, any other concomitant disease or medications used, alcohol/smoking habit were obtained and documented. All these patients were given ondansetron 8 mg with dexamethasone 20 mg and ranitidine 50 mg, intravenously 30 minutes prior to chemotherapy infusion and the same dose repeated after completion of infusion. They were also provided with 8mg ondansetron twice daily for the first five days after chemotherapy. Five millilitres of venous blood were collected and processed under aseptic conditions. Details of occurrence of nausea and vomiting were recorded for the time periods 0-2 hours, 2-24 hours and on days 2-5 after administration of chemotherapy for every participant by means of direct or telephonic interview. Patients were grouped into 'responders' if they had no occurrence of nausea and vomiting and 'non-responders' if they had occurrence of nausea or vomiting. Severity scoring of nausea and vomiting was done using Common Terminology Criteria for Adverse Events (CTCAE) criteria version 4.0 (Supplementary Table 1) and Visual Analogue Scale (VAS). Patients were asked to score their nausea and vomiting severity using VAS for the time periods 0-2 hours, 2-24 hours and on each day from day 2 to day 5. The worst VAS score for each patient scored on any day from day 2 to day 5 was expressed as the VAS score for days 2-5. CTCAEv4.0 grading was done at 24 hours and on each day from day 2 to day 5. In this study, the peak CTCAEv4.0 grade attained on any day from day 2 to day 5 is expressed

as the CTCAEv4.0 grade for days 2-5. The parameters were compared between the genotype groups. The study flow diagram is depicted in Figure 1.



– Visual Analogue Scale, CTCAEv4.0 - Common Terminology Criteria for Adverse Events criteria version 4.0. The worst VAS score for each patient scored on any day from day 2 to day 5 was expres
s VAS score for days 2-5. The peak CTCAEv4.0 grade attained on any day from day 2 to day 5 is expressed as the CTCAEv4.0 grade for days 2-5.

Figure 1. Study flow diagram

Statistics

The baseline characteristics of the study population were expressed as median (range) and in proportions. Baseline demographic characteristics of patients across genotypes were compared using Kruskal-Wallis test for quantitative data and chi-square test for qualitative data. The frequency distribution of allele and genotypes of *ABCB1* genetic polymorphisms were checked for Hardy-Weinberg equilibrium. The comparison between responders and non-responders across genotype groups in the polymorphisms was done using chi-square test. Comparison of episodes of nausea and vomiting and visual analogue scale at different time points across the three genotype groups of *ABCB1* genetic polymorphisms was done using Kruskal-Wallis test for co-dominant model and Mann-Whitney test for recessive model. Proportion of patients in each severity grade of nausea and vomiting (CTCAEv4.0) was compared across genotype groups using chi-square test. Statistical analysis was done using IBM.SPSS statistics software 26.0 Version. $p<0.05$ was considered statistically significant. Haplotype frequencies estimation and linkage disequilibrium analysis were performed by SNPstats software (Institut Català d'Oncologia, Barcelona, Spain).

RESULTS

In this study, 322 cancer patients were screened, out of which 238 patients were recruited as per inclusion-exclusion criteria. During sample processing, adequate DNA could not be extracted from 4 blood samples. The final data set comprised of 234 patients for analysis. In our study population, since prevalence of AA genotype (n=1) in *ABCB1* G2677T/A polymorphism was low; its effects were not studied.

Demographic characteristics

The baseline characteristics of the study population are shown in Table 1. The demographic characteristics were categorised and compared across genotype groups for each polymorphism (Supplementary Tables 2-4). There were no significant differences in the baseline characteristics between genotype groups for *ABCB1 C3435T* and *G2677T/A* polymorphisms. Except for gender (p=0.02), all other characteristics were comparable across genotype groups for *ABCB1 C1236T* polymorphism (Supplementary Table 3).

Table 1. Patient characteristics

Parameters		Values
Age in years	Median (Range)	50 (18-65)
Gender	Male n (%)	103 (44%)
	Female n (%)	131 (56%)
Diagnosis	Cancer cervix, n (%)	107 (45.7%)
	Cancer oropharynx, n (%)	59 (25.2%)
	Cancer hypopharynx, n (%)	21 (9%)
	Germ cell tumour, n (%)	14 (6%)
	Cancer stomach, n (%)	10 (4.3%)
	Cancer lung, n (%)	8 (3.4%)
	Other sites, n (%)	15 (6.4%)
Stage of cancer, n (%)	I	12 (5.1)
	II	76 (32.5)
	III	99 (42.3)
	IV	47 (20.1)
Chemotherapy	Cisplatin monotherapy, n (%)	150 (64.1)
	Cisplatin combination, n (%)	84 (35.9)
	Chemotherapy naive, n (%)	155 (66.2)
	Previous chemotherapy, n (%)	79 (33.8)
Smoking, n (%)		61 (26.1)
Alcoholism, n (%)		36(15.4)
Cisplatin dose, n (%)	40 mg/m^2	96 (41%)
	>40-75 mg/m^2	47 (19.3%)
	>75-100 mg/m^2	91 (38.9)

n = 234

Table 2. Allele and genotype frequency distributions for *ABCB1 C3435T*, *G2677T/A*, *C1236T* polymorphisms among cancer patients in current study

Polymorphism	Genotype	Frequencies	Allele	Frequencies
ABCB1 C3435T	*CC*	0.16	*C*	0.38
	CT	0.5	*T*	0.62
	TT	0.34		
ABCB1 G2677T/A	*GG*	0.13	*G*	0.34
	GT	0.40		
	GA	0.034	*T*	0.59
	TT	0.28		
	TA	0.15	*A*	0.07
	AA	0.004		
ABCB1 C1236T	*CC*	0.16	*C*	0.36
	CT	0.45	*T*	0.64
	TT	0.39		

Frequency distributions of ABCB1 polymorphisms

The frequency distribution of allele and genotype of the patients for *ABCB1 C3435T*, *G2677T/A* and *C1236T* is shown in Table 2. We found that the frequencies of

genotypes for all the studied polymorphisms follow Hardy Weinberg equilibrium. The haplotype frequencies estimation is shown in Table 3. *ABCB1 3435 C>T*, *2677 G>T*, *1236 C>T* genetic variants were assessed for the linkage disequilibrium (LD), *ABCB1 3435 C>T vs 2677 G>T* showed D'=0.69, r=0.68 and *ABCB1 2677 G>T vs 1236 C>T* showed D'=0.93, r=0.89.

Table 3. Haplotype frequencies estimation

S. no	*C3435T*	*G2677T*	*C1236T*	Total	Cumulative frequency	Responders	Non-responders
1	T	T	T	0.5125	0.5125	0.5442	0.3675
2	C	G	C	0.3233	0.8357	0.2727	0.5571
3	C	T	T	0.0753	0.9111	0.0858	0.0254
4	T	G	C	0.0478	0.9589	0.0494	0.0373
5	T	T	C	0.0143	0.9732	0.0179	NA
6	T	G	T	0.0109	0.9841	0.0135	0
7	C	G	T	0.0103	0.9944	0.0128	NA
8	C	T	C	0.0056	1	0.0037	0.0127

Response to therapy with ondansetron for nausea and vomiting following cancer chemotherapy

In the acute phase, 64.5% of all patients had nausea and/or vomiting and 86.3% of all patients had delayed nausea and/or vomiting. Since the number of events for study parameters were low during the time frame 0-2 hours, the analysis of outcomes according to the genotype groups was done for the time periods during 2-24 hours and days 2-5 (Supplementary Table 5). The proportion of patients responding to therapy with ondansetron at different time frames categorised according to various genotypes of *ABCB1* polymorphisms is presented in Tables 4 & 5. The proportions of responders and non-responders with respect to occurrence of nausea were significantly different between the genotype groups for all polymorphisms at three time points studied. Similarly, the proportions of responders and non-responders with respect to vomiting were also significantly different between genotype groups at all time points, with exception for genotypes of *ABCB1 C3435T* on days 2-5 (p=0.08), for which difference was not statistically significant.

Table 4. Proportion of responders and non-responders with respect to nausea and vomiting between ABCB1 genotype groups during 2-24 hours

SNP	Genotypes	Nausea during 2-24 hours		*p* value	Genotypes	Vomiting during 2-24 hours		p value
		Responders, n (%), n=83	Non-Responders, n (%), n=151			Responders, n (%), n=95	Non-Responders, n (%), n=139	
C3435T	***CC***	6 (7.2%)	32 (21.19%)	<0.0001	***CC***	7 (7.37%)	31 (22.3%)	<0.0001
	CT	24 (28.92%)	94 (62.25%)		***CT***	29 (30.53%)	89 (64.03%)	
	TT	53 (63.86%)	25 (30.12%)		***TT***	59 (62.12%)	19 (13.67%)	
C1236T	***CC***	6 (7.23%)	33 (21.85%)	<0.0001	***CC***	7 (7.37%)	32 (23.09%)	<0.0001
	CT	20 (24.1%)	85 (56.29%)		***CT***	27 (28.42%)	78 (56.12%)	
	TT	57 (68.67%)	33 (21.85%)		***TT***	61 (64.2%)	29 (20.86%)	
*G2677T/A**	***GA***	1 (1.2%)	7 (8.43%)	<0.0001	***GA***	1 (1.05%)	7 (5.04%)	<0.0001
	GG	5 (6.02%)	26 (31.33%)		***GG***	5 (5.26%)	26 (18.7%)	
	GT	15 (18.07%)	78 (51.66%)		***GT***	19 (20%)	74 (53.24%)	
	TA	20 (24.1%)	15 (9.93%)		***TA***	24 (25.26%)	11 (7.91%)	
	TT	42 (50.60%)	24 (15.89%)		***TT***	45 (47.37%)	21 (15.11%)	

* Total number of responders and non-responders of *G2677T*/A polymorphism will be 1 less as AA (n=1) has been excluded

Table 5. Proportion of responders and non-responders with respect to nausea and vomiting between ABCB1 genotype groups on days 2-5

SNP	Genotypes	Nausea on days 2-5		*p* value	Genotypes	Vomiting on days 2-5		*p* value
		Responders, n(%), n=33	Non-Responders, n(%), n=201			Responders, n (%), n=32	Non-Responders, n (%), n=202	
C3435T	***CC***	3 (9.1%)	35 (17.41%)	0.021	***CC***	3 (9.4%)	35 (17.33%)	0.08
	CT	15 (45.45%)	103 (51.24%)		***CT***	13 (40.63%)	105 (51.98%)	
	TT	15 (45.45%)	63 (31.34%)		***TT***	16 (50%)	62 (30.69%)	
C1236T	***CC***	4 (12.12%)	35 (17.41%)	0.005	***CC***	3 (9.4%)	36 (17.82%)	0.003
	CT	8 (24.24%)	97 (48.26%)		***CT***	8 (25%)	97 (48.02%)	
	TT	21 (63.64%)	69 (34.33%)		***TT***	21 (65.63%)	69 (34.16%)	
*G2677T/A**	***GA***	1 (3.03%)	7 (3.48%)	0.005	***GA***	0 (0%)	8 (3.96%)	0.0001
	GG	3 (9.1%)	28 (13.93%)		***GG***	2 (6.25%)	29 (14.35%)	
	GT	7 (21.21%)	86 (42.79%)		***GT***	7 (21.88%)	86 (42.57%)	
	TA	3 (9.1%)	32 (15.92%)		***TA***	3 (9.4%)	32 (15.84%)	
	TT	19 (57.58%)	47 (23.38%)		***TT***	19 (59.38%)	47 (23.27%)	

* Total number of responders and non-responders of *G2677T/A* polymorphism will be 1 less as AA (n=1) has been excluded

The effect of *ABCB1 C3435T*, *ABCB1 C1236T* and *ABCB1 G2677T/A* genotypes on the median number of episodes of nausea and vomiting is shown in Table 6 (recessive model) and Supplementary Table 6 (codominant model). The effect of these genotypes on visual analogue score for severity is given in Table 7 (recessive model) and Supplementary Table 7 (codominant model). The comparison of nausea and vomiting severity, graded as per CTCAEv4.0, at 24 hours and days 2-5 of cancer chemotherapy, between the genotype groups for each polymorphism studied is given in Table 8.

TT genotype carriers of all three polymorphisms had significantly lesser incidence of nausea and vomiting when compared to other genotypes combined of the respective polymorphisms during 2-24 hours and days 2-5. Median VAS score for nausea and vomiting was also lower for *TT* genotype carriers at each time point except for nausea on days 2-5 (p=0.057) of *C3435T*. As per CTCAEv4.0, TT genotype carriers had lesser grade at each time point except for days 2-5 nausea (p=0.278) and vomiting (p=0.219) of *C3435T* and nausea on days 2-5 (p=0.068) of *G2677T/A*.

Table 6. Influence of ABCB1 polymorphisms on median number of nausea and vomiting episodes – Recessive Model

SNP	Event	Time after chemotherapy	Median number of episodes (Range)		*p* value
			CC*+*CT n=156	***TT*** n=78	***CC*+*CT*** *vs* ***TT***
C3435T	Nausea	2-24 hours	3 (0-12)	0 (0-5)	<0.0001
		Days 2-5	5 (0-15)	4(0-12)	0.002
	Vomiting	2-24 hours	2 (0-8)	0 (0-2)	<0.0001
		Days 2-5	3 (0-10)	2 (0-8)	0.03
C1236T			***CC*+*CT*** n=144	***TT*** n=90	***CC*+*CT*** *vs* ***TT***
	Nausea	2-24 hours	3 (0-12)	0 (0-4)	<0.001
		Days 2-5	5 (0-15)	3 (0-10)	<0.001
	Vomiting	2-24 hours	2 (0-8)	0 (0-2)	<0.001
		Days 2-5	3 (0-10)	2 (0-8)	0.002
G2677T/A			***GG*+*GT*+*GA*** n=133	***TT*+*TA*** n=101	***GG*+*GT*+*GA*** *vs* ***TT*+*TA***
	Nausea	2-24 hours	4 (0-12)	0 (0-5)	<0.001
		Days 2-5	5 (0-15)	4 (0-12)	<0.001
	Vomiting	2-24 hours	2 (0-8)	0 (0-3)	<0.001
		Days 2-5	3 (0-10)	2 (0-8)	0.003

Table 7. Influence of ABCB1 polymorphisms on median VAS score for nausea and vomiting – Recessive Model

SNP	Event	Time after chemotherapy	Median VAS score (Range)		*p* value
			CC*+*CT n=156	***TT*** n=78	***CC*+*CT*** *vs* ***TT***
C3435T	Nausea	2-24 hours	5 (0-9)	0 (0-6)	<0.0001
		Days 2-5	6 (0-10)	5 (0-9)	0.057
	Vomiting	2-24 hours	4 (0-9)	0 (0-6)	<0.0001
		Days 2-5	5 (0-10)	4.5 (0-9)	0.02
C1236T			***CC*+*CT*** n=144	***TT*** n=90	***CC*+*CT*** *vs* ***TT***
	Nausea	2-24 hours	5 (0-9)	0 (0-6)	<0.001
		Days 2-5	6 (0-10)	5 (0-9)	<0.001
	Vomiting	2-24 hours	4 (0-9)	0 (0-6)	<0.001
		Days 2-5	5 (0-10)	4 (0-10)	0.002
G2677T/A			***GG*+*GT*+*GA*** n=133	***TT*+*TA*** n=101	***GG*+*GT*+*GA*** *vs* ***TT***+TA
	Nausea	2-24 hours	5 (0-9)	0 (0-7)	<0.001
		Days 2-5	6 (0-10)	5 (0-9)	0.011
	Vomiting	2-24 hours	4 (0-9)	0 (0-7)	<0.001
		Days 2-5	5 (0-10)	5 (0-10)	0.027

Table 8. Effect of ABCB1 polymorphisms on severity of nausea and vomiting based on CTCAE criteria at 24 hours and days 2-5 of cancer chemotherapy

SNP	Event	Time	Genotype	CTCAE Grade (n)				*p* value
				0	1	2	3	
C3435T	Nausea	24 hours	***CC***	6	20	11	1	<0.001
			CT	24	65	25	4	
			TT	53	23	2	0	
		Days 2-5	***CC***	3	16	18	1	0.278
			CT	15	55	45	3	
			TT	15	40	23	0	
	Vomiting	24 hours	***CC***	7	19	10	2	<0.001
			CT	29	56	27	6	
			TT	59	19	0	0	
		Days 2-5	***CC***	3	11	13	11	0.219
			CT	13	48	32	25	
			TT	16	27	23	12	
C1236T	Nausea	24 hours	***CC***	6	15	17	1	<0.001
			CT	20	61	20	4	
			TT	57	32	1	0	
		Days 2-5	***CC***	4	13	21	1	0.007
			CT	8	53	42	2	
			TT	21	45	23	1	
	Vomiting	24 hours	***CC***	7	13	15	4	<0.001
			CT	27	52	22	4	
			TT	61	29	0	0	
		Days 2-5	***CC***	3	11	14	11	0.013
			CT	8	40	32	25	
			TT	21	35	22	12	
G2677T/A	Nausea	24 hours	***GG***	5	13	12	1	<0.001
			GT/A	16	57	24	4	
			TT/A	62	38	1	0	
		Days 2-5	***GG***	3	10	17	1	0.068
			GT/A	8	54	37	2	
			TT/A	22	47	31	1	
	Vomiting	24 hours	***GG***	5	14	9	3	<0.001
			GT/A	20	19	27	5	
			TT/A	69	31	1	0	
		Days 2-5	***GG***	2	11	11	7	0.021
			GT/A	7	40	28	26	
			TT/A	22	35	29	15	

DISCUSSION

Nausea and vomiting, the most concerning side-effect of cancer chemotherapy, imparts a significant health and economic burden on the patients and the community. The discovery of a major role played by serotonin in CINV by acting on 5HT3 receptors and the introduction of ondansetron, first 5HT3 receptor antagonist swung the pendulum towards better control of CINV [11,12]. Variability in response to ondansetron has been observed in clinical practice. Genetic variations influencing the pharmacokinetics of ondansetron could explain in part, the variation observed in its anti-emetic efficacy. Ondansetron is a substrate for *ABCB1*-PgP efflux transporter and previous studies had been done to evaluate the effect of *ABCB1* genetic polymorphisms on ondansetron response in ethnically different Indonesian, Japanese, Turkish and Korean populations. [15-17,20].

The allele and genotype frequencies of *ABCB1 C3435T* (C and T allele as 38.4% and 61.6%, respectively, and the distribution of *CC*, *CT*, and *TT* genotypes as 14.5%, 47.7% and 37.8%, respectively) and *G2677T* (G and T allele as 36% and 64%, respectively, and *GG*, *GT*, and *TT* genotypes as 11%, 47.2% and 34.6 %, respectively) have been studied in the South Indian population. Regarding *ABCB1 C1236T*, in Maharashtrian population, the allele and genotype frequencies were given as C and T allele – 38% and 62%,

respectively, and *CC*, *CT*, and *TT* genotypes – 13%, 50% and 37%, respectively. In our study, among the three genetic polymorphisms studied, the frequency distribution of the genotypes of *C3435T* and *C1236T* were similar to previous Indian studies [19,21]. In *G2677T/A* polymorphism, the frequency of *TA* genotype was significantly higher than that observed in the previous study (15% *vs* 4%) [19].

We observed that *ABCB1* genetic polymorphisms had a significant association with the anti-emetic efficacy of ondansetron. Regarding the occurrence of nausea and vomiting in the acute phase, carriers of the *TT* genotype of all three polymorphisms studied, had significantly lesser incidence of nausea and vomiting when compared to other genotypes combined of the respective polymorphisms. Moreover, similar results were obtained in the delayed phase of CINV. Regarding the severity of nausea and vomiting as analysed by visual analogue scale during the acute and delayed phases of CINV, carriers of *TT* genotype in comparison to other genotypes of the respective polymorphisms had significantly lower scores except for nausea on days 2-5 of *C3435T* failing to reach statistical significance (p=0.057), though numerically significant. As per CTCAEv4.0, *TT* genotype carriers had lesser grade at each time point except for days 2-5 nausea and vomiting of *C3435T* and nausea on days 2-5 of *G2677T/A*. Even during these time frames without statistical significance, numerical significance was observed for TT genotype carriers of the specified polymorphisms with grade 0 (no episodes) and grade 1 (mild severity) CTCAEv4.0 compared to higher severity grades. For *C3435T* polymorphism, grade 0 & 1 CTCAEv4.0 nausea on days 2-5 was observed in 50% CC, 59% CT and 70% *TT*, and grade 0 & 1 vomiting on days 2-5 was observed in 37% *CC*, 52% *CT* and 55% *TT*. Regarding *G2677T/A* polymorphism, grade 0 & 1 nausea on days 2-5 was observed in 42% GG, 61% GT/A and 68% *TT/A*. Increasing the sample size would better clarify these statistically insignificant yet numerically significant results.

Babaoglu *et al*. found that in patients (n=216) with *ABCB1 3435 C>T* polymorphism, during the acute CINV phase, the proportion of patients with *TT* genotype were significantly more likely to be emesis free when compared to patients with *CC* genotype, but the difference did not persist in the delayed phase [17].

Choi *et al*. in their study on post- operative patients (n=198), observed that the incidence of post-operative nausea and vomiting was significantly lower in patients with *3435TT* and *2677TT* genotype during the first two hours after surgery, but the difference was not significant across genotypes in the 2-24 hour period. The frequency distribution of ABCB1 2677 genotypes were GG – 21.3%, *GT* – 34.5%, *GA* – 16.8%, *TT* – 13.7%, *TA* – 10.2% and *AA* – 3.6% and for ABCB1 3435 genotypes were *CC* – 40.9%, *CT* – 47.5% and *TT* – 11.6%.16 In a similar study on post-operative patients, Farhat *et al*. observed that in patients with *ABCB1 G2677T* polymorphism, (n=500) the patient group with *TT* genotype had significantly lower incidence of nausea and vomiting during the first 2 hours and also in the 2-24 hour period in contrast to the results of Choi *et al.* [22].

Perwitasari *et al*. found no association between *ABCB1* genetic polymorphisms and anti-emetic efficacy of ondansetron during the acute phase in their study on Indonesian cancer patients (n=202). They did find that in the delayed phase, CTG haplotype carriers had increased incidence of grade 3 and 4 CINV [20].

Hui He *et al*. investigated the association of *ABCB1* genetic polymorphisms (*C3435T* and *G2677T/A*) with the anti-emetic efficacy of ondansetron (n=215). They observed that, during the acute phase, among acute myeloid leukemia patients undergoing cytarabine chemotherapy, with *ABCB1 C3435T* polymorphism, CC genotype had a significant association with high grade vomiting. In haplotype analysis, those patients with *CG* haplotype (*C3435T* and *G2677T/A*) had a higher risk of CINV. However, no such associations were observed during the delayed phase [18].

Regarding ondansetron, *ABCB1*-PgP situated in the blood brain barrier determines the central nervous system drug concentration, whereas that present in the intestinal epithelium serves to regulate the plasma concentration by decreasing the oral absorption (i.e., oral bioavailability) and even for parenterally administered drug, by actively transporting the drug into the gut lumen from the blood stream across the intestinal epithelium. *ABCB1* genetic polymorphisms influence the anti-emetic efficacy of ondansetron by altering the expression and/or function of the efflux transporter. Previous studies have shown that the *3435TT* genotype is associated with altered substrate specificity and reduced transporter activity and *2677TT* is associated with decreased expression of P-glycoprotein [15,23]. In our study, the most responsive to ondansetron were patients with *TT* genotype. Hence, it is conceivable that *TT* genotype was associated with decreased expression and/or transporter function resulting in increased availability of ondansetron at target sites and thus, enhanced anti-emetic efficacy.

To the best of our knowledge, our study is probably the first study in India to investigate the association of *ABCB1* genetic polymorphisms with the anti-emetic efficacy of ondansetron-based medication in cancer chemotherapy patients.

Our study did have few limitations. As it is evident that *ABCB1* genetic polymorphisms influence the anti-emetic efficacy of ondansetron, by causing variation in bioavailability and concentration at target sites, the study would have been more corroborative if drug level of ondansetron in the plasma and cerebrospinal fluid was analysed. Studying only the impact of *ABCB1*-PgP efflux transporter polymorphisms may not be adequate to capture the complete pharmacogenomic influence on the anti-emetic efficacy of ondansetron because genetic polymorphisms in other transporters, target receptors and drug metabolizing enzymes can also play a role in variability in response to ondansetron.

CONCLUSION

Our study revealed a significant association between *ABCB1 C3435T*, *G2677T* and *C1236T* genetic polymorphisms and anti-emetic response to ondansetron-based medication in South Indian cancer patients. However, genetic polymorphisms of other transporters like OCT1, receptor subunits like 5HT3B and drug metabolizing enzyme such as CYP2D6 can also play a role in determining the anti-emetic

efficacy of ondansetron. Hence, further comprehensive studies considering the influence of these variations, together with estimation of ondansetron levels could further enhance the pharmacogenetic knowledge of ondansetron. The results of our study could help in translation of pharmacogenetics into clinical practice if supported by similar studies on other factors influencing the response variability in the same population.

ORCID iDs

Ayyar Porkodi https://orcid.org/0000-0002-0573-9301
Deepak Gopal Shewade https://orcid.org/0000-0001-9993-6551
Goud Alladi Charanraj https://orcid.org/0000-0002-3355-7943

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