Original Article

Polymorphism of the GSTP1 Gene Predicts Oxaliplatin Induced Chronic Neuropathy in South Indian Population

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Abstract

Background: Oxaliplatin-Induced Chronic Neurotoxicity (OXAICN) development with oxaliplatin based therapy in digestive tract cancer patients leads to a decrease in dose or stoppage of the treatment. The study aims to determine whether AGXT, GSTP1, and ABCG2 genetic variants may be associated with the risk of chronic OXAIPN in digestive tract cancer (DTC) patients treated with oxaliplatin based therapy. **Material and Methods:** A total of 228 cancer patients with DTC were enlisted for this study after obtaining ethical approval from the institute's human ethics committee. Peripheral venous blood samples were collected from all the patients, and DNA extraction was done by using the phenol-chloroform method. Genotyping was performed for GSTP1 (rs1695), AGXT (rs4426527), and ABCG2 (rs3114018) genetic variants using real-time polymerase chain reaction with validated real- time TaqMan single-nucleotide polymorphism (SNP) genotyping assays. Neurotoxicity was assessed and graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 4.03. **Results:** The study results found that patients with GSTP1 (rs1695) Ile/Ile (A/A) genotype had significantly higher incidence of severe OXAICN (OR=10.0 (95%CI=2.51-45.75, P=0.005) compared to patients with genotypes of Ile/Val (A/G), Val/Val (G/G) genotypes. AGXT and ABCG2 variants didn't show statistically significant association with the incidence of OXAICN and its severity. **Conclusion:** Our study finding suggests that the genetic variants within the GSTP1 gene might serve as a common biomarker to predict severe OXAICN in the South Indian population treated with oxaliplatin based treatment. However, it requires further validation of our study results in a larger cohort.

Keywords: Digestive tract cancer, South Indian Population, Neurotoxicity, Oxaliplatin, Single Nucleotide Polymorphisms, Medical Oncology, Pharmacogenomics.

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Introduction

Oxaliplatin is one of the effective chemotherapeutic platinum compounds used in the treatment of Digestive Tract Cancers (DTC) in both adjuvant and palliative settings.[1–3] The dose limiting adverse event for this oxaliplatin is chronic peripheral neurotoxicity. Generally, oxaliplatin induced chronic neurotoxicity (OXAICN) is observed after receiving a cumulative dose of 650 mg /m2 and is often a cause for dose modification or stoppage of the therapy as it produces significant discomfort and alters quality of life in these patients.[4–6]

Discovery and validation of the genetic loci that limit the risk of OXAICN are the first steps toward the clinical use of patient genetics in treatment individualization.[7] Various pharmacogenetics studies in literature showed plausible connections between OXAIPN causation and genetic variability in genes that are involved in drug metabolism, detoxification or excretion pathways. Ruzzo et al., study results showed evidence of an association between the GSTP1 105 Val G/G allele and the development of grade 3 neuropathy from oxaliplatin treatment.[8] Additionally, in a study, Lecomte et al., indicated that in a cohort of 64 patients, there was a significant association between the GSTP1 105 Val G/G allele and risk of developing neurotoxicity.[9] In another study, Gamelin et al., found AGXT variant to have significant value of OXAICN.[10]

India is the second most populated nation in the world and the current Indian subpopulations are derived from two paternal races namely the 'Ancestral North Indians' (ANI) and 'Ancestral South Indians'. The Ancestral South Indians are Dravidian speakers and they have distinct genetic signatures compared to other population in the world.[11] As the difference in the distribution of alleles could confound the association between genotype-phenotypes, it is important to study the effect of genetic variants in each population. Therefore, we conducted a prospective study at a tertiary referral medical institution in south

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India with DTC patients to investigate the role of genetic variants in genes that are involved in oxaliplatin metabolism (AGXT), detoxification or excretion pathways (GSTP1, ABCG2) in association with the development of peripheral neuropathy to oxaliplatin- based chemotherapy.

Materials and Methods

Patients: This prospective study included 228 adult patients with DTC who were histologically confirmed and scheduled to receive oxaliplatin based chemotherapy and was carried out between November 2014 and December 2016 at a tertiary care hospital, in collaboration with the departments of Pharmacology, Medical Oncology and Neurology. The inclusion criteria were: Patients aged greater than 18 years, patients with eastern cooperative oncology group performance status (ECOG-PS<2) less than two, patients with normal kidney and liver function tests and diabetic patients with normal electrophysiological values. Pregnant and lactating women, patients receiving other drugs which cause neurotoxicity were excluded from the study.

Assessment of OXAICN: The incidence of chronic OXAIPN was measured and graded with the Common Terminology Criteria for Adverse Events version 4.03 developed by National Cancer Institute (NCI-CTCAE 4.03) which grades the severity of OXAIPN from Zero (no OXAIPN) to Four (severe grade of OXAIPN).

Genotyping and DNA extraction: Before the commencement of therapy with oxaliplatin based regimen, five millilitres of peripheral venous blood was collected from each study subject in tubes containing 10% ethylene diamine tetra acetic acid (EDTA). The genomic DNA from patient blood sample was extracted by using the standard phenol–chloroform extraction method,[12] and was quantified by multianalyzer (TECAN Infinite M200, Switzerland). The genotyping was done on Real- Time Polymerase Chain Reaction (ABI Prism 7300, foster city, CA, USA) by using validated Real-Time TaqMan single nucleotide polymorphism (SNP) genotyping probes (Applied Biosystems, Foster City, CA, USA). All the study samples were evaluated in duplicates along with negative controls to ensure authenticity of the results.

Statistical analyses: The genotypes for each SNP were evaluated as a three-group categorical variable (reference model) and verified for deviation from Hardy–Weinberg equilibrium (HWE). The Fisher's exact test was used to determine the influence of genotype with toxicity groups. Two sided P values of <0.05 were considered statistically significant. All statistical analyses were carried out by using SPSS (Statistical analysis Package for Social Sciences) version 19.0 SPSS (Statistical analysis Package for Social Sciences) version 19.0 and Graph Pad Instat version 3.0 (Graph Pad Software Inc., San Diego, CA, USA).

Results

Patient characteristics: A total of 284 patients who were scheduled to get oxaliplatin based chemotherapy treatment were screened initially and a total of 228 subjects were eventually included in the study between November 2014 and December 2016. The rest, 56 DTC patients were excluded because of meeting the exclusion criteria.

Out of 228 patients with DTC, 111(49%) patients had gastric cancer, 108 (47%) patients had colorectal cancer and 9 (4%) patients had pancreatic and gall bladder cancers. The median age was 53 years (range, 19-75). There were 142 males and 86 females in the study. The detailed demographic and clinical characteristics of the study subjects are given in [Table 1]. All the patients received a mean cumulative dose of 772.8±267.8 mg/m2 of oxaliplatin

The genotype and allele frequencies of studied SNPs and their association with OXAICN in the study cohort: The genotype statuses of the study SNPs were determined for all 228 patients. The details of studied SNPs were given in [Table 2]. The genotype and allele frequencies of all the variants observed in these patients are depicted in [Table 3]. The genotype frequencies of studied SNPs in cases were in Hardy Weinberg equilibrium.

In the present study, genotypes of three SNPs were correlated with the occurrence of OXAICN and its severity. The GSTP1 genetic variant rs1695 was significantly associated with the severe OXAICN. We found no significant association between carriers of rs3114018 (ABCG2), rs4426527 (AGXT) variants with the occurrence and severity of OXAICN in our study cohort [Table 4].

Table 1: Details of studied SNPs of genes GSTP1, ABCG2, AGXT

Gene	SNP type	SNP ID/ rs ID	Allele change	Amino acid change	Gene location	Assay ID (Applied biosystems)
GSTP1	Missense	1695	A/G	ile105Val	Chr.11:67585218	C_3237198_20
ABCG2	Intron	3114018	A/C	-	Chr.4: 88143429	C_9510417_10
AGXT	Missense	4426527	A/G	Ile340met	Chr.2:240878099	C_487386_10

Table 2: Patient characteristics in the study cohort (N=228)

Variable	No. of patients (%)
Age: Median (range), in years	53 (19-75)
Gender:	
Male	142 (62.3)
Female	86 (37.7)
ECOG-PS:	
<1	197 (86.4)
>1	31 (13.6)
Comorbidity status:	
Nil	192 (84.2)

Yes	36 (15.8)
Type of cancer:	
Stomach	111 (48.7)
Colorectal	108 (47.4)
Gall bladder and pancreas	9 (3.9)
Type of chemotherapy:	
Adjuvant	85 (37.3)
Neoadjuvant	30 (13.1)
Palliative	113 (49.6)
Type of regimen:	
CAPOX	123 (53.9)
EOX	76 (33.3)
FOLFOX	20 (8.8)
GEMOX	09 (4.0)
Note: ECOG-PS: Eastern Cooperative Oncology Group Performance Status;	

Table 3: HWE status and genotype frequency of studied SNPs in the study cohort

Gene	SNP ID	Genotyping			alleles		HWE P value
GSTP1	rs1695	AA	AG	GG	A	G	
		85 (37.3)	93 (40.8)	50(21.9)	0.58	0.42	0.19
ABCG2	rs3114018	AA	AC	CC	A	C	
		42 (18.4)	114 (50.0)	72 (31.6)	0.43	0.57	0.61
AGXT	rs4426527	AA	AG	GG	A	G	
		192(84.2)	19 (8.3)	17 (7.5)	0.88	0.12	0.24

HWE - Hardy Weinberg Equilibrium p value.
*p value less than 0.05, significant deviation from Hardy Weinberg Equilibrium

Table 4: Association of GSTP1 (rs1695-A>G), AGXT and ABCG2 variants with the incidence and severity of chronic OXAIPN (N=228)

Gene and Genetic Model		Total no. of patients (%)	Incidence of OXAICN		OR (95%CI)	P value	Severity of OXAICN		OR (95%CI)	P value
			Present, n (%)	Absent, n (%)			Grade 2+3, n (%)	Grade 0+1, n (%)		
GSTP1-rs1695 (A/G)										
Codominant	AA	85 (37.3)	47 (36.2)	38 (38.8)	1.00		25 (43.9)	60 (35.0)	1.00	
	AG	93 (40.8)	61 (46.9)	32 (32.7)	0.64 (0.35-1.18)	0.21	30 (52.6)	63 (36.8)	0.87 (0.46-1.65)	0.8
	GG	50 (21.9)	22 (16.9)	28 (28.5)	0.57 (0.77-3.18)	0.27	2 (3.5)	48 (28.2)	10.0 (2.51-45.75)	0.0008*
Recessive	AA+AG	178 (78.1)	108 (83.1)	70 (71.5)	1.00		55 (96.5)	123 (71.9)	1.00	
	GG	50 (21.9)	22 (16.9)	28 (28.5)	1.96 (0.94-3.7)	0.07	2 (3.5)	48 (28.2)	10.73 (2.51-45.75)	0.0002*
Dominant	GG+AG	143 (62.7)	83 (63.8)	60 (61.2)	1.00		32 (56.1)	111 (65.0)	1.00	
	AA	85 (37.3)	47 (36.2)	38 (38.8)	1.11 (0.65-1.92)	0.78	25 (43.9)	60 (35.0)	0.69 (0.37-1.27)	0.3
Alleles•	A	263 (57.7)	155 (59.6)	108 (55.1)	1.00		80 (70.1)	183 (53.5)	1.00	
	G	193 (42.3)	105 (40.4)	88 (44.6)	1.2 (0.82-1.75)	0.38	34 (29.9)	159 (46.5)	2.04 (1.29-3.22)	0.002*
AGXT-rs4426527 (A/G)										
Codominant	AA	192 (84.2)	108 (83.1)	84 (85.8)	1.00		50 (87.7)	142 (83.0)	1.00	
	AG	19 (8.3)	12 (9.2)	7 (7.1)	0.75 (0.28-1.98)	0.73	04 (7.0)	15 (8.8)	1.32 (0.41-4.16)	0.84
	GG	17 (7.5)	10 (7.7)	7 (7.1)	0.9 (0.32-2.46)	0.83	03 (5.3)	14 (8.2)	1.64 (0.45-5.95)	0.63
Recessive	AA+AG	211 (92.5)	120 (92.3)	91 (92.9)	1.00	0.87	54 (94.7)	157 (91.8)	1.00	
	GG	17 (7.5)	10 (7.7)	7 (7.1)	0.92 (0.33-2.51)		3 (5.3)	14 (8.2)	1.60 (0.44-5.8)	0.66
Dominant	GG+AG	36 (15.8)	22 (16.9)	14 (14.2)	1.00		07 (12.3)	29 (17.0)	1.00	
	AA	192 (84.2)	108 (83.1)	84 (85.8)	1.22 (0.58-2.53)	0.72	50 (87.7)	142 (83.0)	0.68 (0.28-1.66)	0.52
Alleles•	A	403 (88.4)	228 (87.7)	175 (89.3)	1.00		104(91.2)	299 (87.4)	1.00	
	G	53 (11.6)	32 (12.3)	21 (10.7)	0.85 (0.47-1.53)	0.7	10 (8.8)	43 (12.6)	1.49 (0.72-3.08)	0.35
ABCG2- rs3114018 (A/C)										

Codominant	AA	42 (18.4)	28 (21.5)	14 (14.3)	1.00	0.14	11 (19.3)	31 (18.1)	1.00	
	AC	114 (50.0)	58 (44.6)	56 (57.1)	1.93 (0.92-4.02)	0.11	29 (50.9)	85 (49.7)	1.04 (0.46-2.33)	0.92
	CC	72 (31.6)	44 (33.9)	28 (28.6)	1.2 (0.57-2.82)	0.69	17 (29.8)	55 (32.2)	1.14 (0.47-2.76)	0.93
Recessive	AA+AC	156 (68.4)	86 (66.1)	70 (71.4)	1.00		40 (70.2)	116 (67.8)	1.00	
	CC	72 (31.6)	44 (33.9)	28 (28.6)	0.78 (0.44-1.38)	0.48	17 (29.8)	55 (32.2)	1.11 (0.58-2.14)	0.86
Dominant	CC+AC	186 (81.6)	102 (78.5)	84 (85.7)	1.00		46 (80.7)	140 (81.9)	1.00	
	AA	42 (18.4)	28 (21.5)	14 (14.3)	0.6 (0.3-1.22)	0.22	11 (19.3)	31 (18.1)	0.92 (0.93-1.98)	0.84
Alleles•	A	198 (43.4)	114 (43.8)	84 (42.9)	1.00		51 (44.7)	147 (43.0)	1.00	
	C	258 (56.6)	146 (56.2)	112 (57.1)	1.04 (0.71-1.51)	0.9	63 (55.3)	195 (57.0)	1.07 (0.7-1.64)	0.82

Data presented as n (%); OR-odds ratio; CI-confidence interval; • the number of alleles are calculated relative to the total number of chromosomes. * is considered statistically significant.

Discussion

Cancer patients who are receiving chemotherapeutic drugs at clinically relevant doses may not respond in a similar way. There exists inter- individual variability with respect to clinical response and drug-related toxicities. This inter-individual variability is multifactorial contributed by age, gender, ethnicity, nutrition status, co-morbidities, various drug-drug interactions, and genetic factors. Generally, the genetic factors account for about 30% of the inter-individual variations in drug responses. The identification of polymorphisms that impact human diseases and their management has an influence on the medical care. Genetic inheritance has a significant role in inter-individual variation with respect to drug response and toxicity. It will be of remarkable clinical benefits to forecast the drug response before its administration so that clinical effectiveness can be maximized and reduce the treatment related toxicities.[13]

The role of pharmacogenetics in association with drug related response and toxicity had been elucidated previously in the field of oncology. A study by Ma et al has described the correlation between GSTP1- Ile105Val (A>G) with drug related toxicity associated with cisplatin-based therapy in breast cancer patients.[14] There were also similar studies demonstrating the correlation between genetic variants in genes that are involved in the drug transport, detoxification or drug target with the toxicity associated with the platinum drugs.[15,16] Similarly, in this study, we investigated whether the determination of common polymorphisms in genes that are involved in the oxaliplatin metabolism (AGXT), detoxification or excretion pathways (GSTP1, ABCG2) are associated with OXAICN with a sample size of 228 in DTC patients using different genetic model approach like dominant, co-dominant, recessive and additive/multiplicative models.

In our study, patients with GSTP1- Ile/Ile (A/A) genotype had significantly higher incidence of severe OXAICN (OR=10.0 (95%CI=2.51-45.75, P=0.005) compared to patients with genotypes of Ile/Val (A/G), Val/Val (G/G) genotypes [Table 4]. AGXT and ABCG2 variants didn't show any statistical significant association with the incidence of OXAICN and its severity.

Our results were in line with the findings of Ruzzo et al,[8] Lecomte et al,[9] and Inada et al,[17] but discordant with Stoehlmacher et al,[18] and Boige et al,[19] findings where rs1695 variant was not associated with either incidence or severity of chronic OXAIPN. However, Grothey et al reported that Caucasians harbouring a single copy of the mutant allele G or with homozygous GG genotype for GSTP1 (rs1695) variant, were at a higher risk to develop neurotoxicity.[20] In contrast to their report, the observed mutant allele frequency of GSTP1 (rs1695) variant was 43.7% and it did confer significant protection against severe chronic OXAIPN in our population.

In one study, Gamelin et al investigated the association of acute OXAIPN with variants of AGXT gene.[10] They found that patients with the minor allele AGXT haplotype had a significantly higher risk of acute neurotoxicity. In our study we have studied only one AGXT variant namely 1142 A>G (rs4426527) that was also studied by Kanai et al,[21] on Japanese colorectal cancer patients. Our study results are concurrent with Kanai et al study where the AGXT variant not associated with both the incidence and severity of OXAICN. To the best of our knowledge, this is the first study that was carried out the association between GSTP1, AGXT, ABCG 2 polymorphisms and OXAICN. The results demonstrated significant association with the variant of GSTP1 gene and no association with variants of (ABCG2) and AGXT (rs4426527) in this study population.

Conclusion

Our finding suggests that the genetic variants within GSTP1 gene might serve as a common biomarker to predict severe OXAICN in south Indian population who are treated with oxaliplatin based chemotherapy. However, it requires further validation of our study results in a larger cohort.

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Conflicts of interest

There are no conflicts of interest.

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