Personalized Prophylactic Antiemetic Regimens for Control of Chemotherapy-Induced Nausea and Vomiting by Pharmacogenetic Analysis of Three Receptor Genes: *HTR3A*, *HTR3B*, *TACR1*

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ABSTRACT

PURPOSE Contemporary prophylactic antiemetic regimens have improved the control of chemotherapy-induced nausea and vomiting (CINV). However, over 50% of patients still suffer from nausea. This study aimed to correlate the genetic determinants of individual patients with the efficacy of three prophylactic antiemetic regimens.

METHODS Patients with breast cancer in two previously reported prospective antiemetic studies consented for the present pharmacogenetic study. Before high-emetogenic doxorubicin and cyclophosphamide (AC) (neo)adjuvant chemotherapy, they received a combination of antiemetic prophylaxis: regimen A and regimen B were, respectively, aprepitant/ondansetron/dexamethasone with or without olanzapine; regimen C was netupitant/palonosetron/dexamethasone. The effectiveness of antiemetic regimens was mainly assessed by complete protection (CP) rates. Patients' genotypes in three genes, *HTR3A*, *HTR3B* and *TACR1*, were analyzed.

RESULTS Patients who were homozygous TT (p.129Tyr) of a non-nonsynonymous variant in *HTR3B* rs1176744 and homozygous GG of *TACR1* rs3821313 had better outcome with regimen B. Digenic interaction analysis further reveals interaction between rs1176744 and rs3821313. Homozygotes TT of rs1176744 and homozygotes GG of rs3821313 achieved the highest CP rate with regimen B (10/12 patients; 83%), in contrast to only 29% (7/24) with regimen A (P = .0027). Homozygotes GG in both *HTR3A* rs1176722 and *TACR1* rs3821313 showed the poorest response to regimen A with a CP rate of 17% (2/12), whereas patients given regimen B had the highest CP rate (70%; 7/10; P = .0159). The findings were confirmed upon logistic regression adjusted for clinical factors.

CONCLUSION The present study confirmed our hypothesis that among Chinese patients with breast cancer who received AC, the selection of optimal antiemetic prophylaxis may be aided by assessing an individual's pharmacogenetic profile. It also highlights a novel digenic interaction that has not been known before for pharmacogenetic analysis.

ACCOMPANYING CONTENT

Data Sharing Statement

Data Supplement

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INTRODUCTION

Chemotherapy is an important component of antineoplastic strategy. However, chemotherapy-induced nausea and vomiting (CINV) is a common and distressing side effect, affecting patients' treatment outcomes and quality of life.[1] International guidelines have ranked commonly used chemotherapy agents into different emetogenic risks, whereby prophylactic antiemetics could be administered accordingly.[1-5] Olanzapine, by targeting multiple pathways, has been recommended to be added to 5-hydroxytryptamine type 3 (5HT3) and neurokinin-1 (NK1) receptor antagonists plus dexamethasone in the management armamentarium.[6] However, studies assessing the role of adding olanzapine

CONTEXT

Key Objective
Does determination of genetic constitution enable selection of the most effective antiemetic prophylaxis for chemotherapy-induced nausea and vomiting (CINV)?

Knowledge Generated
By applying pharmacogenomic study, homozygotes TT of *HTR3B* rs1176744 and homozygotes GG in *TACR1* rs3821313 were found to have better CINV control when olanzapine is being combined with aprepitant/ondansetron/dexamethasone. Digenic interaction analysis further reveals significant interaction between these genes.

Relevance
Assessment of patients' genetic constitution can enable appropriate selection of the most optimal antiemetic prophylaxis.

have yielded conflicting results.[7-11] This could be due to the fact that such antiemetic regimens are prescribed empirically to nonselected patient population. Complete control of CINV, in particular, those related to symptoms of nausea, is still lacking in a significant proportion of patients. At the same time, it has been well reported that olanzapine, especially when given at a commonly adopted dose of 10 mg, causes side effects of somnolence and higher tendency of non-neutropenic fever.[7-11]

Previous genetic studies on emesis have only focused on the genetic predisposition for CINV or postoperative nausea and vomiting.[12-17] Few studies have evaluated the genetic determinants that could affect the variability in response to antiemetic regimens. 5-HT3 receptors (5HTR3) are expressed in the intestine and play important roles in the sensation of gut fullness and discomfort which relates to normal digestive process.[6] This receptor is an oligomeric complex formed by five subunits, which are encoded by genes *HTR3A*, *HTR3B*, *HTR3C*, *HTR3D*, and *HTR3E*.[18,19] The homomeric receptor formed by five submits of *HTR3A* and heteromeric receptor of *HTR3A*/*HTR3B* showed differences in functional properties and thus are candidate genes for this study. In addition, NK1 receptor, also known as tachykinin receptor 1 (TACR1), is coded by the *TACR1* gene and has also been studied.[16,20] To date, no study has been performed comparing efficacy among different prophylactic CINV regimens in patients with different genotypes in pharmacogenetic receptor genes. Only when multiple regimens are compared could a potential more responsive prophylactic regimen be identified for patients with different genetic makeup.

In this study, we postulated that determination of three genes, *HTR3A*, *HTR3B*, and *TACR1*, may predict the response to a particular antiemetic regimen for an individual patient, thereby enabling personalized selection of optimal antiemetic prophylaxis.

METHODS

Study Design and Participants

Patients in the current pharmacogenomic study participated in two previously reported prospective antiemetic studies for CINV, which were registered at ClinicalTrials.gov (Identifiers: NCT03386617 and NCT03079219, respectively).[11,21] Both studies enrolled similar patient population, that is, Chinese female patients with breast cancer who were chemotherapy-naïve and planning to receive (neo)adjuvant doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 (AC). Study design and efficacy assessment could be obtained from previous reports.[11-21] The antiemetic regimens are listed in the Data Supplement (Table S1). The first study randomly assigned patients to aprepitant/ondansetron/dexamethasone (for the purpose of this report, this is labeled as regimen A) or to aprepitant/ondansetron/dexamethasone with olanzapine (regimen B).[11] The second study evaluated netupitant/palonosetron/dexamethasone (regimen C, with netupitant and palonosetron combined in a capsule known as NEPA).[21] Both studies were approved by the Joint CUHK-NTEC Institutional Review Board of the Chinese University of Hong Kong and Hong Kong Hospital Authority; apart from the main study consent, patients were invited and signed a separate consent for the current study.[20,21]

Assessment of CINV

During the first cycle of AC, CINV assessment included symptoms of vomiting, use of rescue antiemetic medications, and symptoms of nausea (based on a visual analogue scale [VAS] that ranged from 0 to 100 mm).

Nausea was the key issue to be addressed. As a result, two key end points were assessed: complete protection (CP) and no nausea (NN). CP was defined as no vomiting, no use of rescue

therapy, and no significant nausea (NSN) during the study periods. NSN was defined as a nausea VAS of <25 mm, whereas NN was defined as <5 mm. The study period included acute phase (0-24 hours after initiation of AC), delayed phase (24-120 hours), and overall phase (0-120 hours) in the first cycle of AC.

Laboratory Methods for Genotyping

Ten milliliters of peripheral blood was obtained from consented patients. Genomic DNAs were extracted from peripheral blood using commercial kits (FavorPrep, Favorgen cat: FABGK001). Polymerase chain reaction (PCR) was carried out under standard conditions in 96- or 384-well format (AmpliTaq Gold; Thermo Fisher Scientific, Waltham, MA). Three candidate functional single nucleotide polymorphisms (SNPs) of *HTR3A*, *HTR3B*, and *TACR1* were determined (Table 1). Genotyping for SNPs in the candidate genes was carried out by established protocols.[22,23]

Briefly, for PCR-melting genotyping methodology, PCR reactions were carried out in a total volume of 15 μL containing 10 ng of DNA, 10 mM Tris-HCl buffer (pH 8.3), 1.5 mM $MgCl_2$, 200 mM of each deoxynucleotide triphosphate, and 50 ng of primers with different 5′ tails in the presence of Taq DNA polymerase (Roche Molecular Biochemicals, Basel, Switzerland). After PCR, the genotypes of samples were revealed by their melting temperature in the presence of a fluorescent DNA-binding dye such as SYBR Green. DNA samples of known genotypes were included as positive control in each batch of 96-well plates. Results were also confirmed by Sanger sequencing of PCR products. Both positive and negative control samples were included together with replicated samples representing at least 5% of the original sample set. Any genotype data showing departure from Hardy-Weinberg equilibrium were regenotyped by a different protocol.[22,23]

Statistical Analysis

For genetic association analysis, for each treatment regimen, patients' responses (ie, CP or not, as well as NN or not) were used to classify patients into two categorical groups. Thereafter, their genotypes were compared between these two groups in a 2 × 3 table. A statistically significant result indicates that the genotype of that gene polymorphism determines the efficacy of that antiemetic regimen. Besides, the CP and NN rates were compared across various regimens for patients with given genotypes to identify the most effective treatment regimen with the corresponding genotypes. The association between CP, NN, and various genotypes was reported as odds ratio (OR), with 95% CIs and *P* value. Multivariable analysis, adjusting for the clinical factors, was performed. A two-sided *P* value <.05 was considered statistically significant. Statistical analysis was performed on the basis of SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

Patient Characteristics

A total of 180 patients took part in the two clinical studies and received regimen A, B, or C antiemetic prophylaxis; 129 consented for the present pharmacogenomic studies. Forty-five underwent regimen A, 42 received regimen B, and 42 had regimen C. The background characteristics are shown in the Data Supplement (Table S2). The proportion of patients in regimen A versus B versus C who achieved CP after AC was 38%, 57%, and 55%, respectively, whereas that for NN was 33%, 55%, and 52% respectively. Overall, the best efficacy was ~50% with regimens B and C.

Association of SNP Genotypes With Antiemetic Efficacy

Genetic Association Study of Antiemetic Efficacy in Terms of CP

The most robust pharmacogenetic association was found in patients given regimen B, where both *HTR3B* and *TACR1* genotypes influenced the prophylactic efficacy.

Table 2 shows the genetic association between various SNPs of *HTR3B* genotype and treatment response among patients given regimen B. For the overall phase, the T allele (encoding for tyrosine at codon 129 of *HTR3B*) is the common allele of rs1176744 genotypes. This SNP is a nonsynonymous mutation; it is also known as Tyr129Ser (p.Y129S) where the tyrosine of codon 129 is substituted by serine by this T to G nucleotide change. Our results showed that homozygous patients with tyrosine (p.129Tyr/Tyr or TT) were more likely to achieve CP with the four-drug olanzapine-containing regimen; CP rates were 69% (20/29) and 30% (4/13) for TT and GT (p.129Ser/Tyr), respectively (OR, 0.200 [95% CI,

TABLE 1. List of Genes and SNP Studies for Association With Antiemetic Efficacy

Name of Gene	Gene Symbol	SNPs	HGVS Nomenclature
5-hydroxytryptamine receptor 3A, 5-HT3A	*HTR3A*	rs1176722	NC_000011.10:g.113977752G>A
5-hydroxytryptamine receptor 3B, 5-HT3B	*HTR3B*	rs1176744	NP_006019.1:p.Tyr129Ser
Tachykinin receptor 1	*TACR1*	rs3821313	NC_000002.12:g.75092575G>A

Abbreviations: HGVS, Human Genome Variation Society; SNPs, single nucleotide polymorphisms.

TABLE 2. Association Between HTR3B Genotypes and Treatment Efficacy of Regimen B (the olanzapine-containing four-drug regimen)

rs1176744 Genotypes in HTR3B	GT, No. (%)	TT, No. (%)	P^a	OR (95% CI, P^b)
CP in overall phase (0-120 hours)				
Patients did not have CP	9 (70)	9 (31)	.0202	0.200 (0.049 to 0.825, .0260)
Patients achieved CP	4 (30)	20 (69)		
CP in acute phase (0-24 hours)				
Patients did not have CP	7 (54)	6 (21)	.0319	0.224 (0.054 to 0.919, .0377)
Patients achieved CP	6 (46)	23 (79)		
CP in delayed phase (24-120 hours)				
Patients did not have CP	8 (62)	7 (24)	.0204	0.199 (0.049 to 0.810, .0242)
Patients achieved CP	5 (38)	22 (76)		

Abbreviations: CP, complete protection; OR, odds ratio.
[a]*P* value from chi-square test or Fisher exact test.
[b]*P* value from logistic regression.

0.049 to 0.825]; $P = .0260$). When the assessment period is subdivided into acute and delay phases, similar associations were found.

An association was also found between *TACR1* rs3821313 and CP rates for the acute phase among patients in regimen B (Table 3, upper light gray area). As AA genotype is rare (approximately 5%), this genotype is combined with heterozygous GA for analysis (Table 3, lower dark gray area); in other words, the results of the common allele (G) are being analyzed in a recessive mode. Homozygotes GG were more likely to achieve CP during the acute phase (OR, 0.128 [95% CI, 0.024 to 0.687]; $P = .0165$).

Genetic Association Study of Antiemetic Efficacy in Terms of NN

Only one significant association was found in patients who received regimen A (Data Supplement, Table S3, upper light gray area). As homozygous AA of *HTR3A* rs1176722 is rare

TABLE 3. Association Between TACR1 Genotypes and Treatment Efficacy (in terms of CP) of Regimen B (aprepitant/ondansetron/dexamethasone/olanzapine four-drug regimen)

rs3821313 Genotypes in TACR1	AA, No. (%)	GA, No. (%)	GG, No. (%)	P^a
CP in overall phase (0-120 hours)				
Patients did not have CP	1 (25)	11 (58)	6 (32)	.1957
Patients achieved CP	3 (75)	8 (42)	13 (68)	
CP in acute phase (0-24 hours)				
Patients did not have CP	1 (25)	10 (53)	2 (11)	.0187
Patients achieved CP	3 (75)	9 (47)	17 (89)	
CP in delayed phase (24-120 hours)				
Patients did not have CP	0 (0)	10 (53)	5 (26)	.0699
Patients achieved CP	4 (100)	9 (47)	14 (74)	

rs3821313 genotypes in TACR1	AA or GA, No. (%)	GG, No. (%)	OR (95% CI, P^b)
CP in overall phase (0-120 hours)			
Patients did not have CP	12 (52)	6 (32)	0.423 (0.119 to 1.502, .1833)
Patients achieved CP	11 (48)	13 (68)	
CP in acute phase (0-24 hours)			
Patients did not have CP	11 (48)	2 (11)	0.128 (0.024 to 0.687, .0165)
Patients achieved CP	12 (52)	17 (89)	
CP in delayed phase (24-120 hours)			
Patients did not have CP	10 (43)	5 (26)	0.464 (0.125 to 1.725, .2520)
Patients achieved CP	13 (57)	14 (74)	

Abbreviations: CP, complete protection; OR, odds ratio; TACR1, tachykinin receptor 1.
[a]*P* value from chi-square test or Fisher exact test.
[b]*P* value from logistic regression.

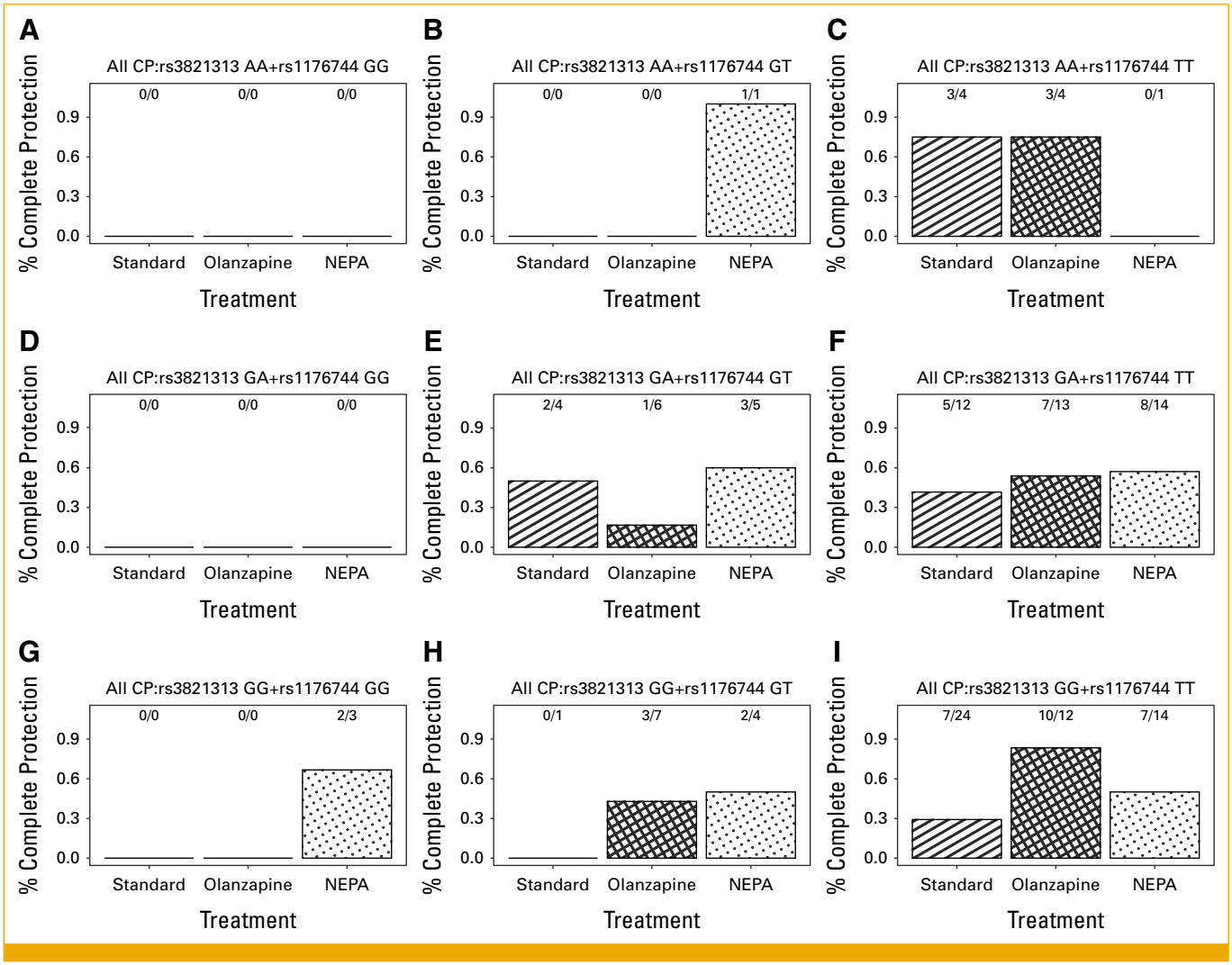

FIG 1. (A-I) Illustrate the interaction between rs1176744 (HTR3B) and rs3821313 (TACR1) and the response to various prophylactic antiemetic treatment regimens in chemotherapy patients (standard: regimen A—aprepitant/ondansetron/dexamethasone; olanzapine: regimen B—olanzapine/aprepitant/ondansetron/dexamethasone; NEPA: regimen C—netupitant/ondansetron/dexamethasone). The ratios of numbers of patients who had CP/number of patients in each group are shown above each bar. The *y*-axis shows the percentage of patients who achieved CP for each regimen. CP, complete protection; TACR1, tachykinin receptor 1.

(<5%), this genotype is combined with heterozygous GA for analysis (Data Supplement, Table S3, lower dark gray area). Homozygotes GG were more likely to have nausea during the overall phase, 83% (19/23) compared with only 50% (11/22) of the non-GG (P = .0252). Similar trends were observed during the acute and delayed phases.

Gene-Gene Interaction in the Prophylactic Treatment of CINV—HTR3B and TACR1 Digenic Genotype Effects

The effects of a combination of genotypes in two SNPs were analyzed. Specifically, only those SNPs with a significant association with treatment efficacy were analyzed. CP in the overall phase was used as the treatment outcome.

The interaction between *HTR3B* rs1176744 and *TACR1* rs3821313 was found to affect antiemetic efficacy. Figure 1 shows the percentage of patients who achieved CP with the three antiemetic regimens. The G allele of rs1176744 and the A allele of rs3821313 were minor alleles of low allelic frequencies, so no patient being homozygous for both were studied (Fig 1A). On the other hand, many patients were both homozygous TT of rs1176744 and homozygous GG of rs3821313 and their treatment efficacy toward the three regimens is shown in Figure 1I. There was a striking difference among the three regimens in terms of CP rates. Patients with this genotypic combination had higher CP rate by regimen B than regimen A (crosshatch and stripe bars, respectively, in Fig 1I); in the overall phase, CP rates were 83.3% (10/12) versus 29%

(7/24), respectively, whereas the corresponding figure with regimen C was 50% (7/14; $P = .0089$).

As the minor alleles of both SNPs are uncommon, the digenic interaction was analyzed by reducing the 3 × 3 genotype combinations into 2 × 2 genotype combinations by combining the homozygous of minor alleles with heterozygous into one class, as shown in Figure 2 (upper left inset). In terms of biology, this assumes that the major alleles act in a recessive manner.[23] The subsequent results confirmed that patients who were homozygous of the common alleles in both SNPs (rs1176744 and rs3821313) had significantly higher CP rate with regimen B than regimen A, 83% versus 29% respectively (crosshatch and stripe bars, respectively, in Fig 2D; $P = .0027$).

On the other hand, patients with combinations of genotypes rs1176744 (GG or GT) and rs3821313 (AA or GA) had the highest CP rate (67%) with regimen C numerically (dotted bar in Figs 2A), compared with regimen A (50%) or B (17%; $P = .2089$).

Gene-Gene Interaction in the Prophylactic Treatment of CINV—HTR3A and TACR1 Digenic Genotype Effects

The interaction between *HTR3A* rs1176722 and *TACR1* rs3821313 also affected antiemetic efficacy. A similar approach was used to combine genotypes of these two SNPs into a 2 × 2 genotype combination figure (Fig 3). Figure 3D showed CP rates in the overall phase. Patients who were homozygous GG in both rs1176722 and rs3821313 showed the poorest response to regimen A (CP rate = 17%; 2/12; stripe bar in Fig 3D), whereas patients given regimen B had the highest CP rate (70%; 7/10; $P = .0159$). Regimen C (CP rate = 46%) was numerically superior to A ($P = .1047$).

On the other hand, patients with combinations of genotypes rs1176722 (AA or GA) and rs3821313 (AA or GA), as shown in Figure 3A, experienced a relatively higher CP rate with regimen C (67%; 2/3; dotted bar in Fig 3A), whereas those of regimens A and B were similar at 46% ($P = .7753$).

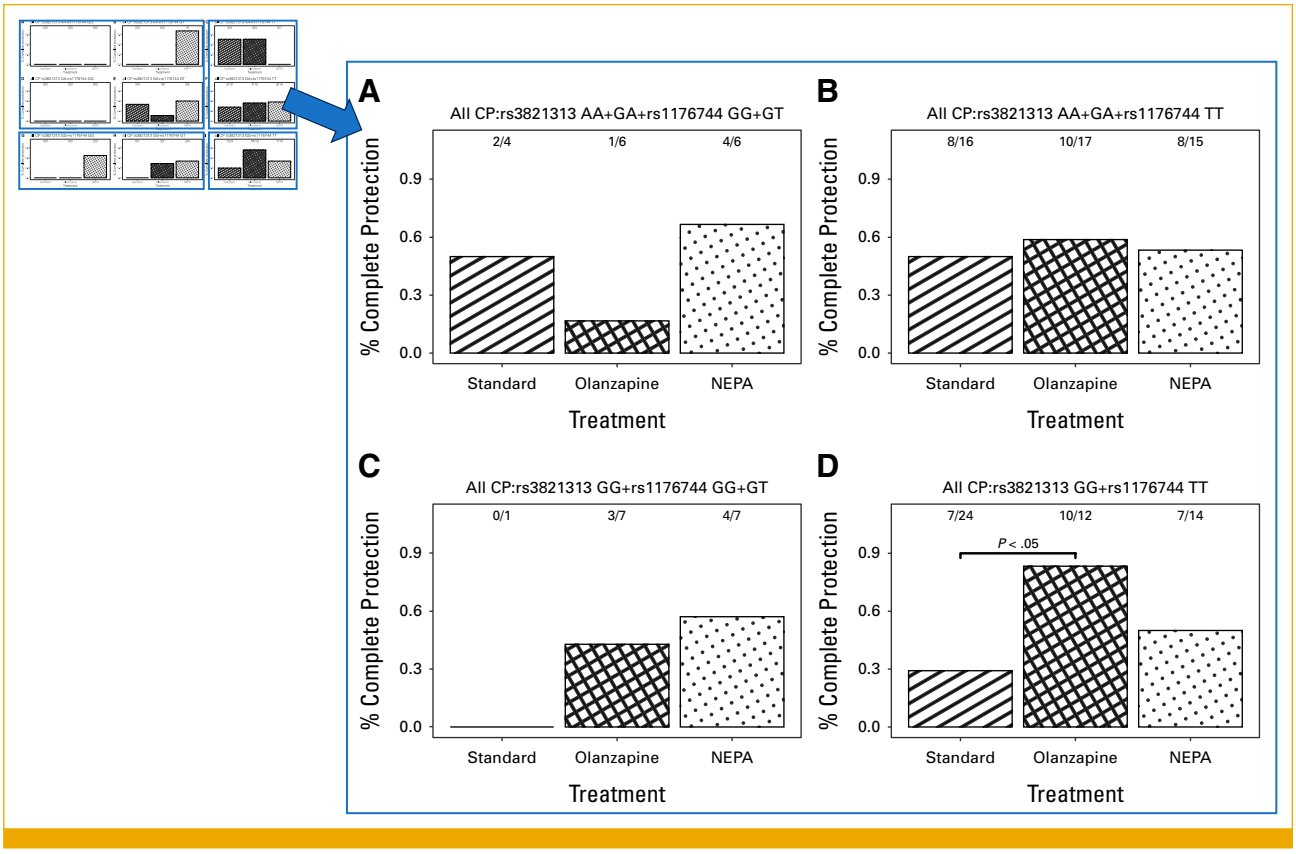

FIG 2. Using a recessive mode to analyze the interaction between rs1176744 (HTR3B) and rs3821313 (TACR1) and response to various prophylactic antiemetic regimens in chemotherapy patients. The *y*-axis shows the percentage of patients who achieved CP for each regimen. Assuming the gene-gene interaction occurs in the homozygotes of both major alleles in a recessive mode, the 3 × 3 combination of genotypes (upper left) is consolidated into four groups of digenic genotypes, as shown in the lower right larger graph (standard: regimen A—aprepitant/ondansetron/dexamethasone; olanzapine: regimen B—olanzapine/aprepitant/ondansetron/dexamethasone; NEPA: regimen C—netupitant/ondansetron/dexamethasone). The ratios of numbers of patients who had CP/number of patients in each group are shown above each bar. (A-C) No significant differences in complete protection was found between different regimens according to the stated genotypes. (D) The *P* value of the statistical comparison between regimen A (standard) and regimen B (olanzapine-containing) is shown. CP, complete protection; TACR1, tachykinin receptor 1.

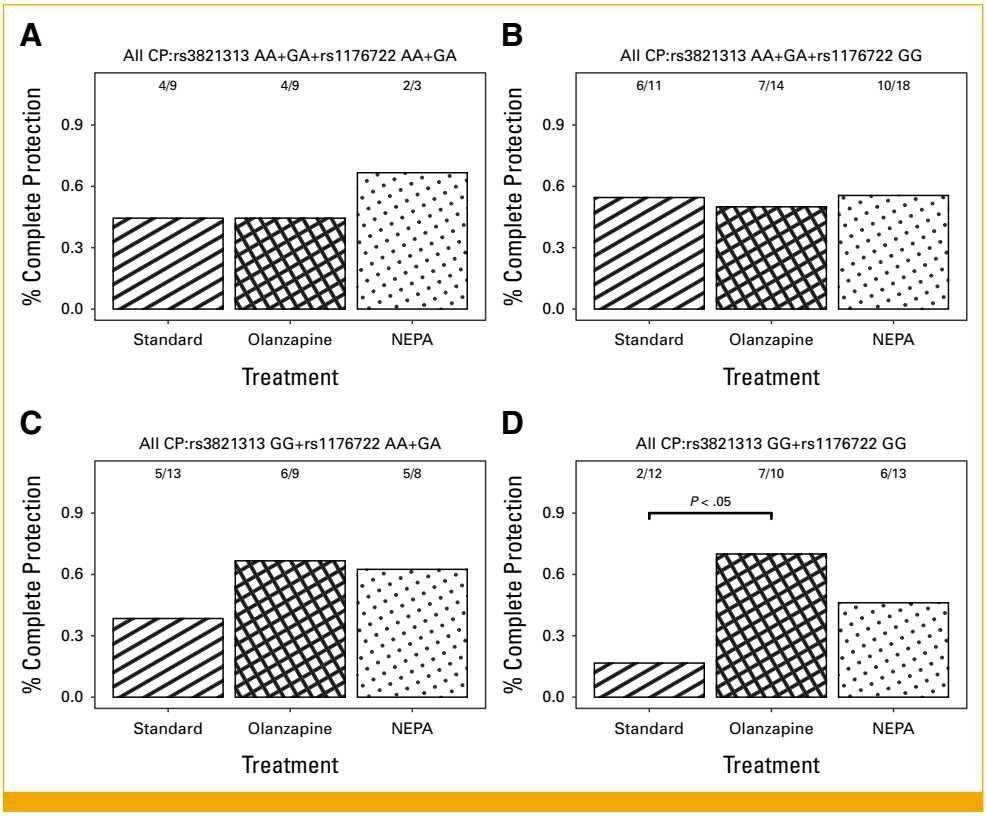

FIG 3. Using a recessive mode to analyze the interaction between rs1176722 (HTR3A) and rs3821313 (TACR1) and response to various prophylactic antiemetic regimens in chemotherapy patients. Assuming the gene-gene interaction occurs in the homozygotes of both major alleles in a recessive mode, the 3 × 3 combination of genotypes of these two SNPs is consolidated into four groups of digenic genotypes as shown here (standard: regimen A—aprepitant/ondansetron/dexamethasone; olanzapine: regimen B—olanzapine/aprepitant/ondansetron/dexamethasone; NEPA: regimen C—netupitant/ondansetron/dexamethasone). The ratios of numbers of patients who had CP/number of patients in each group are shown above each bar. (A-C) No significant differences in complete protection was found between different regimens according to the stated genotypes. (D) The *P* value of the statistical comparison between regimen A (standard) and regimen B (olanzapine-containing) is shown. CP, complete protection; TACR1, tachykinin receptor 1.

Multivariable Analysis of Genetic and Clinical Risk Factors for CINV

The clinical factors in this analysis were based on Tsuji et al[16] and included all well-known factors (Data Supplement, Table S2). Logistic regression revealed that CP rates in all phases among patients who underwent regimen B were significantly higher with homozygous TT of *HTR3B* rs1176744. In addition, homozygotes GG of *TACR1* rs3821313 were associated with significantly higher CP in the acute phase (Data Supplement, Table S4).

DISCUSSION

Our earlier study with the relatively older three-drug regimen of aprepitant/ondansetron/dexamethasone (regimen A) only yielded CP and NN rates of 38% and 33%, respectively. Our study as well as a number of randomized controlled trials has demonstrated that adding olanzapine to this triplet antiemetic regimen (regimen B) could improve CINV[6,7,24]; however, delayed-phase CINV, especially related to nausea, remains to be a distressing symptom, with over 40% of patients not achieving CP and NN.[11,21] Using second-generation NK1- and 5HT3-receptor antagonists such as netupitant/palonosetron/dexamethasone (regimen C), the CP and NN rates were only 55% and 53%, respectively. Furthermore, olanzapine has been well associated with the adverse effects of somnolence and fever.[7-11,20]

Previous genetic studies in relation to CINV have assessed genetic polymorphisms of transporters of central nervous system, drug metabolisms, and target receptors of antiemetic agents in association with risk of CINV, including *ABCB1/ABCB2*, *HTR3A/HTR3B/HTR3C/HTR3D*, and *TACR1*.[12-20,25] These studies have either failed to identify relevant genetic polymorphisms or have inconsistent findings. A meta-analysis with over 2,000 patients analyzed eight polymorphisms in five candidate genes. Only

HTR3C and *ABCB1* polymorphisms were identified to be associated with acute CINV. Such negative findings could be due to the inclusion of a large range of genetic polymorphisms that were evaluated in a heterogeneous group of patient populations who received different chemotherapy of varied emetogenic potential. Furthermore, pharmacogenomic analysis assessing genetic polymorphisms in relation to the effectiveness of specific prophylactic antiemetic regimens has not been well studied. Limited data suggest *TACR1* to be a genetic risk factor for delayed CINV, whereas 5HTR3-related genes showed no significant findings.[16,20]

Our study has some limitations, mainly related to small patient number of one gender receiving one chemotherapeutic regimen only. Nonetheless, the current pharmacogenomic study has several strengths and is unique in a number of ways. A homogeneous population of Chinese ethnicity with breast cancer who were chemotherapy-naïve and receiving AC was prospectively studied ensuring accurate data capturing. As opposed to older antiemetic prophylaxis that involved first-generation (more inferior) NK1-antagonist aprepitant with ondansetron/dexamethasone, this study included more contemporary prophylactic regimens.[26,27] Moreover, the present efficacy analysis focused on important clinical issues of chemotherapy-induced nausea, a symptom that remains to be a challenge. Therefore, two relevant clinical end points were assessed instead of using the commonly assessed complete response (defined as no vomiting and no use of rescue therapy): nausea per se as well as CP (which encompasses symptoms of nausea plus complete response).

Several findings were clinically relevant in this study. First, among patients receiving regimen B, homozygotes TT of *HTR3B* rs1176744 achieved a significantly higher CP rate during all phases of CINV. Second, homozygotes GG of *TACR1* rs3821313 also achieved significantly higher CP in the acute phase. These pharmacogenomic findings remain to be significant upon multivariable analysis. On the other hand, using regimen A, homozygotes GG of *HTR3A* rs1176722 had significantly higher rates of nausea during the overall and delayed phases. Finally, the current genetic findings did not affect the efficacy of regimen C, where the CP rates were 50% or above irrespective of genotypic compositions.

Furthermore, since it is well known in the field of animal breeding that epistasis may occur and phenotypes may also be determined by the effect of two genes,[28,29] gene-gene interaction in association with antiemetic efficacy was assessed.[23,28,29] Digenic genotype interaction study between *HTR3B* rs1176744 and *TACR1* rs3821313 revealed that homozygotes TT of rs1176744 and homozygotes GG of rs3821313 were best treated by regimen B (CP rate = 83%), whereas CINV was least controlled by regimen A (CP rate = 29%). Conversely, for homozygotes GG in both rs1176722 and rs3821313, regimen A should be avoided since it provided the lowest CP rate (17%), whereas regimen B, providing a CP rate of 70%, could be recommended. Additionally, although not statistically significant, patients with combinations of genotypes rs1176722 (AA or GA) and rs3821313 (AA or GA), as well as those with combinations of genotypes rs1176744 (GG or GT) and rs3821313 (AA or GA), had the highest CP rates with regimen C. Finally, irrespective of the genotypic variation, regimen C has consistently shown to outperform regimen A in the current genotypic analysis (Figs 2 and 3). These findings suggest that among patients with genotypic assessment revealing rs1176744 (GG or GT) or rs1176722 (AA or GA) in combination with rs3821313 (AA or GA), regimen C is the preferred antiemetic prophylaxis. Moreover, in the absence of pharmacogenetics analysis, regimen C could be regarded as a relatively more acceptable antiemetic regimen.[30–32] The Data Supplement (Table S5) tabulates the above suggested antiemetic prophylaxis regimens in accordance with genotypic variables. Although we observed the potential digenic interaction in this study, it is possible that it may occur even under single gene effect, as is evident that *HTR3B* rs1176744 was associated with CP by itself in logistic regression.

In conclusion, in addition to clinical- and treatment-related profiles, a personalized approach with the incorporation of pharmacogenomic analysis is warranted in the prevention of CINV. The current study supports the notion that pharmacogenomic analysis is feasible and could be an important element in precision medicine. In addition to symptoms of vomiting, future studies should focus on symptoms related to nausea. A hybrid combination of regimens B and C, for instance, with netupitant/palonosetron/dexamethasone and olanzapine in selected patient population based on pharmacogenetic analysis should be tested to further optimize antiemetic prophylaxis.

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DISCLAIMER

The funder of the study had no role in study design, data collection, data analysis, data interpretation, decision to publish, or manuscript preparation.

PRIOR PRESENTATION

Preprint version available on medRxiv (https://www.medrxiv.org/content/10.1101/2024.12.29.24319754v1).

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DATA SHARING STATEMENT

A data sharing statement provided by the authors is available with this article at DOI https://doi.org/10.1200/PO-24-00858. All data relevant to the study are included in the article or uploaded as supplementary information. The data are available from the Comprehensive Cancer Trials Unit of the Department of Clinical Oncology, Chinese University of Hong Kong, but restrictions apply to the availability of these data. These data were used under permission for the current study, and so are not publicly available. Data are, however, available from the authors (WY and FM) upon reasonable request. Data will be made available for 15 years from the start of the clinical trials.

AUTHOR CONTRIBUTIONS

Conception and design: Winnie Yeo, Nelson L.S. Tang
Financial support: Winnie Yeo
Administrative support: Winnie Yeo, Kwai T. Lai
Provision of study materials or patients: Winnie Yeo, Thomas K.H. Lau, Kwai T. Lai, Elizabeth Pang
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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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