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**Original Article**

# Association of *ABCB1*, *5-HT3B* Receptor and *CYP2D6* Genetic Polymorphisms with Ondansetron and Metoclopramide Antiemetic Response in Indonesian Cancer Patients Treated with Highly Emetogenic Chemotherapy

**Dyah A. Perwitasari[1,2,3], Judith A.M. Wessels[2], Robert J.H.M. van der Straaten[2], Renee F. Baak-Pablo[2], Mustofa Mustofa[3], Mohammad Hakimi[4], Johann W.R. Nortier[5], Hans Gelderblom[5] and Henk-Jan Guchelaar[2,*]**

[1]Department of Pharmacy, Ahmad Dahlan University, Yogyakarta, Indonesia, [2]Department of Clinical Pharmacy and Toxicology, Leiden University Medical Center (LUMC), Leiden, The Netherlands, [3]Department of Pharmacology and Therapy, Universitas Gadjah Mada, [4]Department of Obstetric and Gynaecology, Universitas Gadjah Mada, Yogyakarta, Indonesia and [5]Department of Clinical Oncology, LUMC, Leiden, The Netherlands

*For reprints and all correspondence: H-J. Guchelaar, Department of Clinical Pharmacy and Toxicology, Leiden University Medical Center, PO Box 9600, NL 2300 RC Leiden, The Netherlands. E-mail: h.j.guchelaar@lumc.nl

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**Objective:** Suboptimal treatment of chemotherapy-induced nausea and vomiting and unsatisfactory response to antiemetic drugs cause impairment of cancer patient's daily functioning. This study was aimed to investigate the association of selected germline polymorphisms with ondansetron and metoclopramide response in Indonesian cancer patients treated with highly emetogenic chemotherapy.

**Methods:** We enrolled 202 chemotherapy naïve patients treated with cisplatin at a dosage of $\geq$50 mg/m$^2$ as monotherapy or as combined chemotherapy. Ondansetron 8 mg and dexamethasone 8 mg intravenously were the standard antiemetic therapy for prevention of acute chemotherapy-induced nausea and vomiting. Metoclopramide 10 mg orally, three times per day as fixed prescription, was given until 5 days after chemotherapy to prevent delayed chemotherapy-induced nausea and vomiting. Primary and secondary outcomes were the occurrence of chemotherapy-induced nausea and vomiting in the acute and delayed phase. The following single-nucleotide polymorphisms were determined in ABCB1: rs1045642, rs2032582 and rs1128503; in *5-HT3B-R*: rs45460698, rs4938058 and rs7943062; and in *CYP2D6*: rs16947 (*CYP2D6*2*), rs3892097 (*CYP2D6*4*) and rs1065852 (*CYP2D6*10*) using Taqman assays.

**Results:** During the acute phase, 21.8 and 30.2% patients experienced Grade 3 and 4 nausea and vomiting, respectively, whereas 38.6% patients experienced nausea and/or vomiting in the delayed phase. Carriers of the CTG haplotype of the *ABCB1* gene experienced Grade 3 and 4 chemotherapy-induced nausea and vomiting more often than other haplotypes in the delayed phase ($P < 0.05$). No associations were found with the *5-HT3B* receptor haplotypes and CYP2D6-predicted phenotypes.

**Conclusions:** Our study shows that in Indonesian cancer patients treated with highly cytostatic emetogenic, carriership of the CTG haplotype of the *ABCB1* gene is related to an increased risk of delayed chemotherapy-induced nausea and vomiting.

*Key words: pharmacogenetics – antiemetics – chemotherapy – cancer – Indonesia*

## INTRODUCTION

Chemotherapy-induced nausea and vomiting (CINV) is the most common side effect of cancer patients treated with highly emetogenic chemotherapy (1) and has a significant effect on the patients' daily functioning and well-being (2). Poor control of acute CINV, which occurs within 24 h after chemotherapy, may be used as a predictor of delayed CINV (3). However, patients with delayed CINV, which persists from 24 to 120 h after chemotherapy, experience more severe impact of daily functioning than patients with acute CINV (4).

The introduction of 5-hydroxytriptamine-3 receptor antagonists (5-HT3RAs) significantly improved the control of CINV (4). However, the use of 5-HT3RAs in combination with dexamethasone as an antiemetic treatment in patients treated with highly emetogenic chemotherapy provides only 70–80% complete protection in the acute phase (2,6) and 60% complete protection in delayed emesis (5).

Ondansetron is the first 5-HT3RA and the most widely used in Indonesia community hospitals. Standard antiemetic treatment for prevention of acute CINV in Indonesia is ondansetron in combination with dexamethasone. For prevention of delayed CINV, metoclopramide is given orally from 24 until 120 h after chemotherapy. We realize that the combination of a 5-HT3RA, a neurokinin 1 antagonist and a corticosteroid is more effective and is therefore frequently given to cancer patients treated with high emetogenic chemotherapy (6,7). This combination increases the complete protection of acute emesis, with 10–15% increased response in comparison with the combination of a 5-HT3RA and a corticosteroid (8,9); currently, the neurokinin 1 antagonist aprepitant is not available in Indonesia.

Next to the antiemetic treatment regimen, patient characteristics such as age, gender, history of motion sickness and history of alcohol drinking are known to influence antiemetic drug efficacy. In addition, in recent years, it appeared that also genetic variation in genes encoding drug transporters, metabolic enzymes and drug targets may influence drug efficacy (3). Indeed, variability in ondansetron transport, biotransformation and receptor affinity may cause variations in ondansetron's efficacy (10). More specifically, ondansetron is transported into the blood–brain barrier by the drug transporter P-glycoprotein (P-gP) and is partially metabolized by, for example, cytochrome P450 2D6 (CYP2D6) and has moderate affinity on the 5-HT3 receptors (10–12).

In a previous study, it has been reported that the gene *ABCB1*-encoding P-gP has a role in the pharmacology of ondansetron. The ondansetron transepithelial transport decreased when an inhibiting agent was added into an MDR1 cell line. In other words, the passive diffusion rate of ondansetron was increased by P-gP (13). This mechanism was found in both the gastrointestinal and blood–brain barrier (11,12). In addition, a polymorphism in the *ABCB1* gene, 3435C>T, showed a significant association with the occurrence of acute CINV in cancer patients (13). Regarding ondansetron metabolism, it was reported in a Caucasian population that the ultrarapid metabolizers (UMs) of CYP2D6 experienced the most severe nausea and vomiting after chemotherapy treatment (14). It has been shown that ondansetron is mainly metabolized by CYP1A2, CYP2D6 and CYP3A4 (15). Finally, other studies suggested that variation of 5-HT3B, 5-HT3C and 5-HTR3D receptors could be the predictors of 5-HT3RAs' efficacy in cancer patients (16–18).

For metoclopramide, gene variations of the protein transporter and the drug-metabolizing enzyme are suggested to influence efficacy and adverse drug reaction (19,20). The passage of metoclopramide across the blood–brain barrier is also influenced by the P-gP transporter (19), whereas its metabolism is highly dependent on CYP2D6 (20,21).

In theory, not only the response to antiemetic drugs may be genetically determined but also the susceptibility to emetogenic drugs leading to interindividual differences in vomiting and nausea at baseline. However, as our knowledge, there are no studies relating genetic variants to severity of chemotherapy-induced emesis. The aim of this study was to investigate the association of *ABCB1*, *5-HT3B* receptor polymorphisms and CYP2D6-predicted phenotypes with ondansetron and metoclopramide antiemetic response of Indonesian cancer patients treated with highly emetogenic chemotherapy.

## PATIENTS AND METHODS

### Study Population

The study population involved various cancer patients in the Oncology Department of Dr Sardjito Hospital, Yogyakarta, Indonesia, from January 2009 until April 2010, who were treated with cisplatin at a dosage of $\geq 50\ mg/m^2$ as monotherapy or in combination chemotherapy regimens. Ondansetron 8 mg and dexamethasone 8 mg intravenously were the standard antiemetic therapy for prevention of acute CINV. Metoclopramide, 10 mg orally, three times per day as fixed prescription, was given to the patients after cytostatic administration until 5 days after chemotherapy in order to prevent delayed CINV.

Patients were eligible for this study if they were $\geq 18$ years old with a Karnofsky performance scale of $\geq 50\%$. We used self-reported ethnicity. However, to make a more accurate assessment of ethnicity, the ethnicity of the parents and grandparents also were verified. Exclusion criteria were: the presence of nausea or vomiting 24 h before chemotherapy; the use of other antiemetics such as benzodiazepines or neuroleptics, radiotherapy within 24 h before the start of chemotherapy; the use of opioids within the last 2 weeks, the use of inducers of CYP3A4 or inhibitors of CYP2D6; patients with concomitant diseases that might cause nausea or vomiting (e.g. ulcerations or obstruction of the upper gastrointestinal system, aspartate aminotransferase/alanine aminotransferase $>2.5\times$ ULN for patients without liver

metastases and >5× ULN for patients with liver metastases, renal dysfunction defined by creatinine clearance <60 ml/min, brain metastases, artificial stoma or pregnancy).

This study has been approved by The Ethical Committee of the Medical Faculty of Universitas Gadjah Mada, Yogyakarta, Indonesia. All of the patients signed the consent form before enrollment.

### Nausea and Vomiting Assessment

Every patient completed a daily record up to 5 days starting at initiation of cytotoxic drugs administration. The daily record contained the number of episodes of vomiting, the 0–100 scale of nausea visual analog scale (NVAS) and the antiemetic therapy that was consumed over 5 days. Patients were informed that an episode of vomiting that was separated at least 1 min from the previous one counted as a single episode (22).

### Study Outcome Definitions

The primary outcome was acute nausea and vomiting which was categorized based on the National Cancer Institute Common Toxicity Criteria v.3 (NCI CTC v.3) (23). We grouped the acute nausea and vomiting into Grade 1–2 and Grade 3–4 nausea and vomiting. Patients were discharged from the hospital on day 1, a few hours after the cytostatic administration. Therefore, we could not categorize the secondary outcome based on the NCI CTC v.3. The secondary outcome was delayed nausea and vomiting scored dichotomic (yes or no). Patients without delayed emesis (no) were defined as patients without vomiting and/or had <5 score on the NVAS scale, while patients with delayed emesis (yes) were defined as patients with vomiting and/or scored ≥5 scale of NVAS (24,25).

### Single-nucleotide Polymorphism Selection and Genotyping Assays

Three single-nucleotide polymorphisms (SNPs) in the *5-HT3B* receptor gene: rs45460698 (deletion AAG in 5′-UTR position), rs4938058 (intron) and rs7943062 (3′ near gene); three SNPs in the *ABCB1* gene: rs1045642 (exon 26), rs2032582 (exon 22) and rs1128503 (exon 12); and three SNPs of *CYP2D6*; rs16947 (CYP2D6*2), rs3892097 (CYP2D6*4) and rs1065852 (CYP2D6*10) were selected from the National Center for Biotechnology Information SNP database. The selection of the SNPs was based on the following criteria: a minor allele frequency of >0.2, a validated SNP according to the NCBI database, and preferably a perfect linkage disequilibrium (LD) with other SNPs (for 5-HTR3B receptor gene: $D'- = 1$ and $r^2 \geq 0.7$) and/or indications for relevance based on previous publications (18,26–29).

DNA was extracted from saliva samples. DNA was quantified using Nanodrop (Isogen, Maarssen, The Netherlands). Genotypes were established using commercially available pre-designed Taqman assays and analyzed on ABI 7500 real-time PCR System from Applied Biosystems (Nieuwerkerk aan den IJssel, The Netherlands) according to the manufacturer' protocol of allelic discrimination. As a quality control, at least 5% of samples were genotyped in duplicate and no inconsistencies were found. The overall genotyping success rate of the samples was more than 96%.

### Statistical Methods

The genotype frequencies were assessed for deviations from the Hardy–Weinberg equilibrium and they did not deviate from the Hardy–Weinberg equilibrium. The gPlink software was used to estimate the haplotype frequency and to set the individual haplotypes from raw genotype data. The estimation of haplotype frequencies/phases was ≥0.01 and phase consideration was ≥0.01 (30).

The predicted phenotypes of SNPs in the *CYP2D6* gene were defined as follows: CYP26*2 is an active allele, *10 is a decreased activity allele and *4 is a defective allele (14,31,32). Therefore, the definitions of extensive metabolizers (EMs) include *2/*2 and *2/*10; the intermediate metabolizers (IMs) include *2/*4, *4/*10 and *10/*10; and poor metabolizers (PMs) include *4/*4.

The $\chi^2$ test was performed to test the association of patient characteristics and primary and secondary outcome.

Moreover, the association of 5-HT3B receptor and ABCB1 haplotypes and CYP2D6-predicted phenotypes with primary and secondary outcome were analyzed by $\chi^2$ test. These associations are considered to be the result of ondansetron as the antiemetic drug in the acute phase and metoclopramide as the antiemetic drug in the delayed phase. A $P$ value of <0.05 was considered as a significant association. This study is explorative and hypothesis-generating, and therefore, we decided not to correct for multiple testing.

## RESULTS

A total of 202 patients were enrolled in this study. Table 1 presents the patient characteristics. The most frequent diagnosis was cervical cancer (59.9%), mostly diagnosed as Stage 1 or 2 of cancer (68.8%). The majority of the patients (90.6%) were treated with an intermediate dose of cisplatin (50–70 mg/m$^2$) either as monotherapy or in combination therapy, and the remaining patients (9.4%) were treated with cisplatin at a dosage of 75–100 mg/m$^2$.

The presence of nausea and vomiting during the acute and delayed phase is presented in Table 2. In the acute phase, 21.8% patients experienced acute nausea and 30.2% patients experienced acute vomiting, whereas 38.6% patients experienced nausea and/or vomiting in the delayed phase. Figures 1 and 2 present the means of vomiting episodes and NVAS score over 5 days. The peak of vomiting episodes and NVAS score was seen on day 2, with a gradual decline afterwards.

**Table 1.** Characteristics of cancer patients treated with antiemetics ($n = 202$)

| Characteristic | *n* | % |
|---|---|---|
| Age (mean ± SD) | 48.6 ± 9.6 | |
| Gender | | |
| Male | 14 | 6.9 |
| Female | 188 | 93.1 |
| Diagnosis | | |
| Cervical cancer | 121 | 59.9 |
| Ovarian cancer | 58 | 28.7 |
| Lung cancer | 3 | 1.6 |
| Nasopharyngeal cancer | 13 | 6.4 |
| Vulva cancer | 7 | 3.4 |
| Stages of cancer | | |
| Stages I and II | 139 | 68.8 |
| Stages III and IV | 63 | 31.2 |
| Cytostatic agent | | |
| Cisplatin | 81 | 40.1 |
| Cisplatin and other agent | 121 | 59.9 |
| Cisplatin dose (mg/m$^2$) | | |
| 50–70 | 183 | 90.6 |
| 75–100 | 19 | 9.4 |
| BMI | | |
| Underweight (16–18.5 kg/m$^2$) | 49 | 24.3 |
| Normal (>18.5–25 kg/m$^2$) | 117 | 57.9 |
| Overweight and obese (>25 kg/m$^2$) | 36 | 17.8 |
| Karnofsky performance status | | |
| 80–100% | 182 | 90.1 |
| 50–70% | 20 | 9.9 |
| Co-morbidity | | |
| None | 109 | 53.9 |
| At least 1 | 93 | 46.1 |
| History of motion sickness | | |
| Yes | 39 | 19.3 |
| No | 163 | 80.7 |
| History of morning sickness during pregnancy | | |
| Yes | 45 | 22.3 |
| No | 134 | 66.3 |
| Patients' perception for having nausea and vomiting after chemotherapy | | |
| Yes | 79 | 39.1 |
| No | 123 | 60.9 |
| Anxiety | | |
| Yes | 90 | 44.6 |
| No | 112 | 55.4 |

SD, standard deviation; BMI, body mass index; NA, not applicable because patients have not been pregnant yet.

**Table 2.** The occurrence of acute and delayed chemotherapy-induced nausea and vomiting

| | *n* | % |
|---|---|---|
| Acute nausea | | |
| Grades 1 and 2 | 158 | 78.2 |
| Grades 3 and 4 | 44 | 21.8 |
| Acute vomiting | | |
| Grades 1 and 2 | 141 | 69.8 |
| Grades 3 and 4 | 61 | 30.2 |
| Delayed CINV | | |
| None | 124 | 61.4 |
| Yes | 78 | 38.6 |

CINV, chemotherapy induced nausea and vomiting.

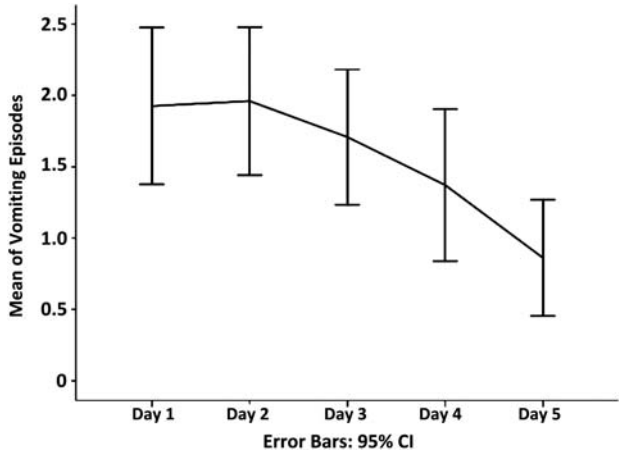


**Figure 1.** Mean (± SD) number of vomiting episodes over 5 days after initiation of chemotherapy.

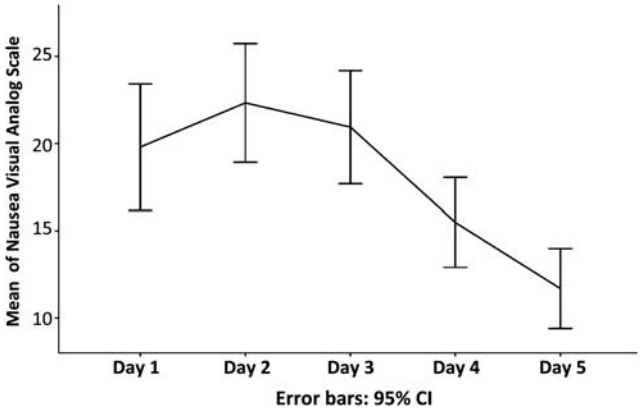


**Figure 2.** Mean (± SD) of nausea visual analog scale over 5 days after initiation of chemotherapy.

Table 3 depicts the association between patient characteristics and primary and secondary outcome measurements. No significant associations of patient characteristics and primary

**Table 3.** Univariate analysis of patient characteristics and primary secondary outcome

| Patient characteristics | Acute nausea [*n* (%)] | | *P* value | Acute vomiting [*n* (%)] | | *P* value | Delayed CINV [*n* (%)] | | *P* value |
|---|---|---|---|---|---|---|---|---|---|
| | Grades 1 and 2 ($n = 158$) | Grades 3 and 4 ($n = 44$) | | Grades 1 and 2 ($n = 141$) | Grades 3 and 4 ($n = 61$) | | None ($n = 78$) | Yes ($n = 124$) | |
| Age (mean ± SD) | 48.4 ± 9.9 | 47.7 ± 8.8 | 0.67 | 48.6 ± 9.4 | 47.6 ± 10.0 | 0.51 | 48.8 ± 9.8 | 47.4 ± 9.4 | 0.29 |
| Gender | | | | | | | | | |
| Male | 12 (8.2) | 1 (2.3) | 0.20 | 10 (7.1) | 3 (6.6) | 0.75 | 115 (8.1) | 74 (5.1) | 0.55 |
| Female | 146 (91.8) | 43 (97.7) | | 131 (92.9) | 58 (93.4) | | 9 (91.9) | 4 (94.9) | |
| Diagnosis | | | | | | | | | |
| Cervical cancer | 95 (60.1) | 26 (59.1) | 0.86 | 88 (62.4) | 33 (54.1) | 0.46 | 79 (63.7) | 42 (53.8) | 0.31 |
| Ovarian cancer | 46 (29.1) | 12 (27.3) | | 39 (27.7) | 19 (31.1) | | 41 (25.0) | 27 (34.6) | |
| Others | 17 (10.8) | 6 (13.6) | | 14 (9.9) | 9 (14.8) | | 13 (11.3) | 9 (11.5) | |
| Stage of cancer | | | | | | | | | |
| Stages I and II | 106 (67.1) | 33 (75.0) | 0.32 | 94 (66.7) | 45 (73.8) | 0.32 | 86 (69.4) | 53 (67.9) | 0.83 |
| Stages III and IV | 52 (32.9) | 11 (25.0) | | 47 (33.3) | 16 (26.2) | | 38 (30.6) | 25 (32.1) | |
| Cytostatic agent | | | | | | | | | |
| Cisplatin | 59 (37.3) | 22 (50.5) | 0.13 | 56 (39.7) | 25 (41.0) | 0.87 | 53 (42.7) | 28 (35.9) | 0.33 |
| Cisplatin + other agents | 99 (62.7) | 22 (50.0) | | 85 (60.3) | 36 (59.0) | | 71 (57.3) | 50 (64.1) | |
| Cisplatin dose | | | | | | | | | |
| $<$50–70 mg/m$^2$ | 143 (90.5) | 40 (90.9) | 0.93 | 130 (92.2) | 53 (86.9) | 0.24 | 114 (91.9) | 69 (88.5) | 0.41 |
| 75–100 mg/m$^2$ | 15 (9.5) | 4 (9.1) | | 11 (7.8) | 8 (13.1) | | 10 (8.1) | 9 (11.5) | |
| BMI | | | | | | | | | |
| Underweight ($<$16 kg/m$^2$) | 42 (26.6) | 7 (15.9) | 0.16 | 38 (27.0) | 11 (18.0) | 0.05 | 27 (21.8) | 22 (28.2) | 0.15 |
| Normal (16–18.5 kg/m$^2$) | 86 (54.4) | 31 (70.5) | | 74 (52.5) | 43 (70.5) | | 70 (56.5) | 47 (50.3) | |
| Overweight and Obese ($>$18.5 kg/m$^2$) | 30 (19.0) | 6 (13.6) | | 29 (20.6 | 7 (11.5) | | 27 (21.8) | 89 (11.5) | |
| Karnofsky performance status | | | | | | | | | |
| 80–100% | 143 (90.5) | 39 (88.6) | 0.71 | 129 (91.5) | 53 (86.9) | 0.95 | 113 (91.1) | 69 (88.5) | 0.54 |
| 50–70% | 15 (9.5) | 5 (11.4) | | 12 (8.5) | 8 (13.1) | | 11 (8.9) | 9 (11.5) | |
| Co-morbidity | | | | | | | | | |
| None | 83 (52.5) | 26 (59.1) | 0.44 | 74 (52.5) | 35 (57.4) | 0.52 | 70 (66.9) | 39 (50.0) | 0.37 |
| At least 1 | 75 (47.5) | 18 (40.9) | | 67 (47.5) | 26 (42.6) | | 54 (33.1) | 39 (50.0) | |
| Motion sickness history | | | | | | | | | |
| No | 131 (82.9) | 32 (72.7) | 0.13 | 119 (84.4) | 44 (72.1) | 0.09 | 103 (83.1) | 60 (76.9) | 0.28 |
| Yes | 27 (17.1) | 12 (27.3) | | 22 (15.6) | 17 (27.9) | | 21 (16.9) | 18 (23.1) | |
| Morning sickness history | | | | | | | | | |
| No | 106 (67.1) | 28 (63.6) | 0.23 | 99 (70.2) | 35 (57.4) | 0.13 | 84 (67.7) | 50 (64.1) | 0.27 |
| Yes | 32 (20.3) | 13 (29.5) | | 27 (19.1) | 18 (29.5) | | 21 (19.4) | 21 (26.9) | |
| NA | 20 (12.7) | 3 (6.8) | | 15 (10.6) | 8 (13.1) | | 16 (12.9) | 7 (9.0) | |
| Patients' perception for NV after chemotherapy | | | | | | | | | |
| No | 97 (61.4) | 26 (59.1) | 0.78 | 91 (64.5) | 32 (52.5) | 0.11 | 74 (59.7) | 49 (62.8) | 0.66 |
| Yes | 61 (38.6) | 18 (40.9) | | 50 (35.5) | 29 (47.5) | | 50 (40.3) | 29 (37.2) | |
| Anxiety | | | | | | | | | |
| No | 84 (53.2) | 28 (63.6) | 0.21 | 77 (54.6) | 35 (57.4) | 0.72 | 68 (54.8) | 44 (56.4) | 0.83 |
| Yes | 74 (46.8) | 16 (36.4) | | 64 (45.4) | 26 (42.6) | | 56 (45.2) | 34 (43.6) | |

**Table 4.** Univariate analysis of gene haplotypes and primary–secondary outcome

| Gene | Acute nausea [*n* (%)] | | *P* value | Acute vomiting [*n* (%)] | | *P* value | Delayed CINV [*n* (%)] | | *P* value |
|---|---|---|---|---|---|---|---|---|---|
| | Grades 1 and 2 | Grades 3 and 4 | | Grades 1 and 2 | Grades 3 and 4 | | None | Yes | |
| ABCB1 gene | $n = 150$ | $n = 38$ | | $n = 136$ | $n = 52$ | | $n = 119$ | $n = 69$ | |
| CCG | | | | | | | | | |
| Other haplotypes | 87 (58.0) | 23 (60.5) | 0.78 | 82 (60.3) | 28 (53.8) | 0.42 | 67 (56.3) | 43 (62.3) | 0.42 |
| Carrier of CCG haplotype | 63 (42.0) | 15 (39.5) | | 54 (39.7) | 24 (46.2) | | 52 (43.7) | 26 (37.3) | |
| CTG | | | | | | | | | |
| Other haplotypes | 76 (50.7) | 22 (57.9) | 0.43 | 68 (50.0) | 30 (57.7) | 0.35 | 70 (58.8) | 28 (40.6) | 0.02[a] |
| Carrier of CTG haplotype | 74 (49.3) | 16 (42.1) | | 68 (50.0) | 22 (42.3) | | 49 (41.2) | 41 (59.4) | |
| CTT | | | | | | | | | |
| Other haplotypes | 138 (92.0) | 38 (100.0) | 0.07 | 125 (91.9) | 51 (98.1) | 0.12 | 109 (91.6) | 67 (97.1) | 0.14 |
| Carrier of CTT haplotype | 12 (8.0) | 0 (0.0) | | 11 (8.1) | 1 (1.9) | | 10 (8.4) | 2 (2.9) | |
| TTT | | | | | | | | | |
| Other haplotypes | 60 (40.0) | 12 (31.6) | 0.34 | 53 (39.0) | 19 (36.5) | 0.76 | 46 (38.7) | 26 (37.7) | 0.90 |
| Carrier of TTT haplotype | 90 (60.0) | 26 (68.4) | | 83 (61.0) | 33 (63.5) | | 73 (61.3) | 43 (62.3) | |
| 5HT3B gene | $n = 150$ | $n = 36$ | | $n = 131$ | $n = 55$ | | | | |
| AAGAG | | | | | | | | | |
| Other haplotypes | 34 (22.7) | 10 (27.8) | 0.52 | 32 (24.4) | 12 (21.8) | 0.70 | | | |
| Carrier of AAGAG haplotype | 116 (77.3) | 26 (72.2) | | 99 (75.6) | 43 (78.2) | | | | |
| AAGGG | | | | | | | | | |
| Other haplotypes | 106 (70.7) | 21 (58.3) | 0.15 | 87 (66.4) | 40 (72.7) | 0.40 | | | |
| Carrier of AAGGG haplotype | 44 (29.3) | 15 (41.7) | | 44 (33.6) | 15 (27.3) | | | | |
| AAGAA | | | | | | | | | |
| Other haplotypes | 112 (74.7) | 30 (83.3) | 0.28 | 99 (75.6) | 43 (78.2) | 0.70 | | | |
| Carrier of AAGAA haplotype | 38 (25.3) | 6 (16.7) | | 32 (24.4) | 12 (21.8) | | | | |
| Del AG | | | | | | | | | |
| Other haplotypes | 107 (71.3) | 26 (72.2) | 0.92 | 96 (73.3) | 37 (67.3) | 0.41 | | | |
| Carrier of del AG haplotype | 43 (28.7) | 10 (27.8) | | 35 (26.7) | 18 (32.7) | | | | |
| CYP2D6-predicted phenotype | $n = 150$ | $n = 37$ | | $n = 133$ | $n = 54$ | | $n = 117$ | $n = 70$ | |
| EM | 93 (62.0) | 28 (75.7) | 0.12 | 86 (64.7) | 35 (64.8) | 0.98 | 76 (65.0) | 45 (64.3) | 0.93 |
| IM | 57 (38.0) | 9 (24.3) | | 47 (35.3) | 19 (35.2) | | 41 (35.0) | 25 (35.7) | |

EM, extensive metabolizers; IM, intermediate metabolizers.
[a]Significant value.

or secondary endpoint were found. However, the data suggest that Grade 3 and 4 acute CINV and delayed CINV are more frequent in younger patients with low performance and a history of motion sickness but the associations did not reach significance. The statistical analyses were performed in the female subjects to understand the association between gene variants, patients' characteristic and the primary/secondary outcome. However, we found no significant association in the analysis results (data not shown).

In Table 4, the association of gene haplotypes and phenotypes with primary and secondary endpoint are presented. A statistical significant association was found between the CTG haplotype in the *ABCB1* gene and the presence of nausea and vomiting in the delayed phase. Carriers of the *ABCB1* CTG haplotype experienced more frequent Grade 3/4 CINV compared with the other haplotypes ($P < 0.05$). Multivariate analysis demonstrated that age and gender did not alter this result (data not shown).

In our population, no predicted phenotypes of CYP2D6, the UMs or PMs were found; the percentages of EMs and IMs were 59.9 and 32.7%, respectively.

## DISCUSSION

Our study confirms that prevention of CINV is suboptimal, and ondansetron and dexamethasone could prevent ~80% of the patients from acute nausea and 70% of the patients from acute vomiting. In the delayed phase, with metoclopramide, 60% of the patients experienced no nausea and/or vomiting. These percentages are lower than commonly seen with newer antiemetic drugs such as aprepitant or with the use of 5HT3RAs for prevention during the delayed phase, but these are no standard therapies in Indonesia.

To date, the reasons of variability in antiemetic drug response are largely unknown. To some extent, patient characteristic such as age and gender may contribute to variable drug response. Although we did not find significant association between patient characteristic and primary or secondary outcome in this study, a non-significant trend analysis supported that young patients were more susceptible to experience higher grade of acute and delayed nausea and vomiting. A previous study in cancer patients showed that female gender and younger age were associated with higher risk of CINV (9). A reason for not replicating these findings in our study is that our patients were mostly women, of relatively young age and with a narrow distribution of age, resulting in limited power to find associations with gender and age. Remarkably, patient-related risk factors such as age play no role in individualizing choice of antiemetic treatment in patients treated with highly emetogenic chemotherapy (33).

Variations in genes which are involved in the pharmacology of antiemetic drugs may explain interpatient variability in response to these drugs. Indeed, our study shows that carriership of the CTG haplotype in the *ABCB1* gene increases the risk of delayed CINV and may therefore modify the effect of metoclopramide. In contrast, our study shows that genetic variants in *ABCB1*, *5-HT3B* receptor and *CYP2D6* are not related to ondansetron efficacy in acute CINV.

Interestingly, while the CTG haplotype of *ABCB1* is related to delayed CINV, it is not related to acute CINV. This could be explained by the mechanism of cisplatin-induced nausea and vomiting which is probably mostly mediated by the serotonin release in the gastrointestinal enterochromaffin cells and not in the central nervous system (34). Thus, the haplotype of *ABCB1* which could theoretically increase the amount of ondansetron that crosses the blood–brain barrier did not show significant impact in the ondansetron response. However, in a previous pharmacogenetic study in Caucasian cancer patients, it was shown that the TT genotype of 3435C>T of *ABCB1* experienced less severe of emesis, because it was supposed that higher concentrations of ondansetron were available in the central nervous system (13).

The significant association between the carrier of the CTG haplotype in the *ABCB1* gene and delayed nausea vomiting indicates that metoclopramide efficacy is modified by the *ABCB1* gene variation. The proposed mechanism is that passage of metoclopramide across the blood–brain barrier is increased in the absence of an active P-gP. Indeed, metoclopramide's site of action as an antiemetic is thought to be in the fourth ventricle, which is located behind the blood–brain barrier. The role of P-gP in metoclopramide transport in the central nervous system is consistent with the finding of and increased metoclopramide concentration in the central nervous system in patients with an inactive P-gP leading to extra pyramidal symptoms (19).

In the current study, the percentage of patients who experienced acute nausea and vomiting seemed to be higher in carriers of the AAGAG haplotype in the 5-HT3B receptor gene, although it did not reach statistical significance. Patients carrying the deletion AAG haplotype in the 5-HT3B receptor experienced a lower grade of nausea and a higher grade of vomiting in the acute phase compared with the other haplotypes.

We performed a haplotype analysis because we could consider information about human evolutionary history and genetic variants by finding the LD (35). Previous studies in Caucasian cancer patients used the genotype of 3435C>T of the *ABCB1* gene and the -100_-102 AAG deletion variant of the *5-HTR3B* gene and performed an association analysis rather than a haplotype analysis (13,18). Therefore, we cannot compare our study findings with the previous studies in Caucasian cancer patients. Teh et al. reported that the allele frequencies in 3435C>T of the *ABCB1* gene were different between Asians and Caucasians.

Among our patients, no predicted phenotypes of CYP2D6 PMs or UMs were identified and the frequency of EMs exceeded that of IMs. Similar results were found in a previous study in healthy subjects of Malaysian Chinese origin, presenting that there were no PM and the frequency of EM in this population was also around 60% (31). Indeed, in subjects of Asian origin, the PM phenotype is very rare. The previous study of Kaiser et al. in Caucasian cancer patients showed that a different antiemetic response to ondansetron was found in both CYP2D6 UMs and PMs. The PMs and UMs showed the lowest and the highest score of nausea and vomiting in the acute phase, respectively (14). Since the incidence of predicted phenotypes of CYP2D6 PMs and UMs in subjects with Indonesian origin is very low, the role of the CYP2D6 phenotype in explaining variability in ondansetron and metoclopramide efficacy in Asians seems to be limited if present at all.

While there are two reports suggesting that CYP2D6 has a significant role in metoclopramide metabolism (20,21), we found no association between CYP2D6-predicted phenotype and metoclopramide efficacy. The EMs and IMs as the only predicted phenotypes found in our study may be the reasons for these results.

In conclusion, our study suggests that the carriers of the CTG haplotype of the *ABCB1* gene have increased risk of

CINV during the delayed phase. However, variants in the genes encoding ABCB1, CYP2D6 and 5-HT3B receptor are not associated with antiemetic efficacy of ondansetron in Asian cancer patients during the acute phase. Further studies are needed to confirm the application of these results in clinical practice.

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## Conflict of interest statement

None declared.

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