

RESEARCH COMMUNICATION

Genetic Polymorphisms in the Three Malaysian Races Effect Granisetron Clinical Antiemetic Actions in Breast Cancer Patients Receiving Chemotherapy

Bassam Abdul Rasool Hassan*, Zuraidah Binti Mohd Yusoff

Abstract

Introduction: Nausea and vomiting are recognized as two separate and distinct conditions with a wide spectrum of etiologies either directly associated with cancer itself or its treatment. According to the new ranking of chemotherapy side effects, nausea is the number one or the most disturbing side effects while vomiting is the third and sometimes the fifth. The introduction of 5-HT₃-receptor antagonists in the early of 1990s has revolutionized the treatment of nausea and vomiting, these agents remaining the mainstay of antiemetic therapy today. Ethnic variation (due to genetic polymorphisms) may lead to diversity in antiemetic treatment pharmacokinetic and pharmacodynamic properties, in terms of distribution, elimination, disposition and clinical effects. The aim of the present study was to clarify genetic polymorphism effects in the three main races in Malaysia i.e., Malay, Chinese and Indian, on the clinical antiemetic effects of granisetron. **Methods:** In this longitudinal prospective observational study, 158 breast cancer patients treated with chemotherapy were monitored for nausea and vomiting in the first 24 hours after chemotherapy administration. The patients were then followed up again after 3 to 5 days of chemotherapy. **Results:** Genetic polymorphisms in the three races in Malaysia have significant effect on granisetron clinical antiemetic action because each is characterized by variant CYP3A4 enzymatic action. **Conclusion:** According to the result, different type of 5-HT₃ receptor antagonists, such as tropisetron and dolasetron which are predominantly metabolized by CYP2D6, should be used especially for Chinese breast cancer patients.

Keywords: Acute and delayed nausea and vomiting - genetic polymorphisms - CYP3A4 - granisetron

Asian Pacific J Cancer Prev, 12, 185-191

Introduction

Interindividual diversity in drug metabolism is caused by many factors including environmental factors, cultural factors related with type of diet, concomitant drug therapy as well as genetic factors i.e., ethnic variation. All of these variations play an important role in changing pharmacokinetic and pharmacodynamic properties, volume of distribution, elimination, disposition and clinical effect for many drugs (Gross et al., 1999; Ruzilawati et al., 2007). Much of this distinction, has shown to be caused by genetic polymorphisms of the human cytochrome P450 enzymes (CYP) (Ruzilawati et al., 2007). CYP is the most vital enzymatic system concerned with drug metabolism. Approximately 65% of common drugs used are metabolized by cytochrome P450 enzymes and half of them are mediated by the CYP3A subfamily (Ruzilawati et al., 2007). The CYP3A subfamily consists of 4 members: CYP3A4, CYP3A5, CYP3A7 and CYP3A47 and represents about 30% of the total CYP in the human liver. The most superior subfamily among the 4 types that play the major role in metabolism

of more than 60% of all drugs used in human is CYP3A4 (Ruzilawati et al., 2007). Miscellaneous CYP3A4 alleles in the population may partake in interindividual variability in CYP3A4 activity (Ruzilawati et al., 2007).

In case of cancer patients nausea and vomiting can be clinically significant and severely incapacitating side effects of cytotoxic chemotherapy (Aapro, 2004). These symptoms can symbolize a major therapeutic challenge and if unsatisfactorily controlled by antiemetic treatment, will limit a patient's ability or desire to eat and drink, considerably reduce quality of life, threaten the success of therapy, and result in increased mortality, morbidity, and prominently health care costs (Aapro, 2004). The management of nausea and vomiting has enhanced greatly in recent years, with the utilization of 5-hydroxytryptamine₃ (5-HT₃, serotonin₃)-receptor antagonists (Bloechl-Daum et al., 2006). These agents in combination with corticosteroids have been instrumental in improving the control of vomiting among patients receiving chemotherapy (Bloechl-Daum et al., 2006).

All 5-HT₃ receptor antagonists are metabolized by the cytochrome P-450 enzymes: tropisetron and dolasetron

Clinical Pharmacy Discipline, School of Pharmaceutical Sciences, University Sains Malaysia, Minden Penang, Malaysia *For correspondence : bassamsunny@yahoo.com

predominantly by CYP2D6, ondansetron partially by CYP2D6 but also by CYP3A4, CYP2E1, or CYP1A2, and granisetron mainly by CYP3A4 (Kaiser et al., 2002). Even so there is significant percentage of cancer patients who do not respond well to 5-HT₃ receptor antagonists. The most important cause for such individual variation in drug response may be differentiation in drug biotransformation by genetically polymorphic enzymes, such as the hepatic cytochrome P-450 enzyme subfamily (Kaiser et al., 2002).

Granisetron is an influential and highly selective 5-HT₃-receptor antagonist that has little or no attraction for other 5-HT receptors, or dopaminergic, adrenergic, benzodiazepine, histaminic, or opioid receptors. In contrast, other 5-HT₃-receptor antagonists have affinities for diverse receptor-binding sites (Bloechl-Daum et al., 2006). For example, ondansetron has obvious binding to 5-HT_{1B}, 5-HT_{1C} and μ -opioid receptor sites. Although not proven, the binding of these agents to extra receptor subtypes other than their target receptor may lie beneath the inferior adverse-event profile seen with ondansetron compared with granisetron (Bloechl-Daum et al., 2006).

In the present study, we try to investigate the genetic polymorphisms effect of the three races in Malaysia i.e., Malay, Chinese, Indian on the clinical antiemetic effect of granisetron. Also it will investigate the action or the effect of the main risk factors which play role in CINV which are patients anxiety, patients history of motion sickness, cancer stages and consumption of alcohol.

Materials and Methods

Study design and setting

This is a longitudinal prospective observational study, conducted in a government hospital on Penang island i.e., Penang General Hospital which is the biggest public hospital in Penang. Penang island is located in the northwest of Malaysia and is separated from the west-coast of Malaysia by five kilometer channel. The approval letter for this study was issued by one of the research institute under the National Institutes of Health (NIH). These are the Institute for Medical Research (IMR), Clinical Research Centre (CRC), Institute of Public Health (IPH), Institute for Health Management (IHM), Institute for Health Systems Research (IHSR), and Institute for Health Behavioral Research (IHBR). Approved was also issued by Ministry of Health Malaysia (MOH). All mentioned above are with the declaration of Helsinki 1995 (as revised in Tokyo in 2004).

The current study try to find the association between the clinical action of granisetron in palliating and/ or preventing of acute and/ or delayed nausea and vomiting caused by chemotherapy with the onset and/ or severity of acute and delayed nausea and vomiting that will take place among the three main Malaysian races (Malay, Chinese, Indian) (Gross et al., 1999; Bernard et al., 2006). Pharmacologically it has been significantly proven that the three ethnic groups in Malaysia are phenotypical and genotypical variant from each others, i.e., polymorphisms of CYP3A4 among Malaysian subjects has been described. Clinical relevance of these genetic variants in these healthy volunteers is under investigation (Ruzilawati et al., 2007;

Yang et al., 2004). So this present study will try to find whether these variations have an effect on granisetron clinical action or not.

Patients

This study was conducted among adult patient (≥ 18 years old) with breast cancer, regardless of tumor stage admitted to wards C11 or C19 in Penang Hospital and were treated with chemotherapy only. These patients were monitored till the cessation of their chemotherapy administration or until a maximum of 1 cycle of chemotherapy treatment completed. During this stage all the required data were collected by direct interview (person-to-person) and from patients files whereby information related with demographic data and clinical data were collected. The direct interview helped to collect accurate data which are amenable to qualitative methodology. This direct interview was carried out after getting the patients consent.

Data collection

Data collection sheet used was structured interview form containing mixed questions developed based on standardized questions from a global standard model which is The Morrow Assessment of Nausea and Emesis (MANE). The reliability of the questionnaire that used by this study was tested by using Person and Cronbach's alpha test after a pilot study on 40 breast cancer patients who suffered from nausea and vomiting. The results showed that it was reliable since its Cronbach's alpha was high (0.910). While the validity of its face and content was conducted by exploring the opinion of a panel of expert and consultant in Penang Hospital.

This study involved patients admitted to the oncology ward (C11 or C19) in Penang Hospital during this study period. The sample size for this study was calculated by using the PS: power and sample size program (Dupont and Plummer, 2004), with a standard calculation at a significant level of 0.05 and confidence interval 95%. The sample size required for this study with power of 95% was 158 breast cancer patients. In this study, breast cancer patients who were treated with chemotherapy were monitored and data on information related with onset and severity of acute nausea and vomiting were collected. Then the patients were followed up after 3 to 5 days of chemotherapy treatment to collect information related to the onset and severity of delayed nausea and vomiting.

The variables collected in this part of the study include data on patient demography, breast cancer stages, nausea (classification and onset, severity of acute nausea, severity of delay nausea), vomiting (classification and onset, severity of acute vomiting, severity of delay vomiting), anxiety (present or not), history of motion sickness (present or not), social support (present or not), history of chemotherapy in inducing nausea and vomiting in previous cycles, educational level and consumption of alcohol. In addition, information was obtained on the chemotherapy including the type of chemotherapy regimen and cycles. Data on antiemetic treatment used to control acute and/ or delayed nausea and vomiting were also collected.

Statistical analysis

The type of data collected include categorical data which were non-normally distributed this was confirmed with the Statistical Package of Social Sciences (SPSS®) software program version 15 thus non parametric test were used to analyze them. The data were entered into the SPSS® software program version 15 for analysis. The type of statistical test used was Chi-square because as mentioned above, the type of data collected was categorical and not normally distributed. In addition, this study was an observational study looking for association hence this test will be applied. This test mainly depends on the frequency of the variables, since Chi-square required frequency for each cell to give a dependable result of not less than 5 times. Also data showing frequency lower than 5 times must not be more than 20% of the total data. The results were considered significant when $P < 0.05$ with confidence interval of 95%. The power for this study was more than 95%.

Results

Patient characteristics

The main result of this study was the demographic data as shown in Table 1. All the breast cancer patients (n=158) were women. Most of them (n=126; 79.7%) had an early-stage disease and a small number (n=32; 20.3%) had advanced -stage disease. Chinese were the predominant race (n=101, 63.9%), followed by Malay (n=35, 22.2%) and finally the Indian (n=22, 13.9%). Their mean age was 52.4 years (range, 26-73 years). Majority (n=53; 33.5%) were patients between 50-59 years old. As seen in Table 2, the majority of the patients did not suffer from anxiety (n=107; 67.7%) or motion sickness (n=145; 91.7%). Also the majority of them had social support either from their husband or their family (n=115; 73%), 110 (82.6%) patients showed a history of previous chemotherapy cycles with nausea while 99 (74.8%) show history of vomiting. Majority of them did not consume alcohol (n=124; 78.5%). As for their education level, the majority had a diploma (n=61; 38.5%) followed by those who finished secondary school (n=42; 26.6%), bachelor (n=29; 18.4%), primary school (n=21; 13.3%) then post graduate (n=2; 1.3%) while very few were not educated (n=3; 1.9%). One hundred and forty seven patients (n=147; 93%) were treated with cyclophosphamide + epirubicin + 5-fluorouracil (FEC), while 6 (3.8%) were treated with cyclophosphamide + adriamycin +5-fluorouracil (CAF) and 5 (3.2%) received cyclophosphamide + methotrexate + 5-fluorouracil (CMF).

All the patients were given a 5-HT3 antagonist (e.g., granisetron) and dexamethasone combination as premedication as well as metoclopramide and dexamethasone tablets as postmedication.

Prevalence of CINV

About half of the Chinese patients (n=45; 44.6%) suffered from acute and delayed CINV. Twelve (12, 11.9%) of them suffered from acute nausea and delayed nausea and vomiting, 5 (4.9%) showed acute nausea and vomiting and delayed vomiting, those who show

Table 1. Demographic and Clinical Data for the Breast Cancer Patients

Demographic data	Value
Female (gender)	158 (100%)
< 50 year	74 (46.8%)
≥ 50 year	84 (53.2%)
Mean age (range)	52.4 years (26-73 years)
Race	
Chinese	101 (63.9%)
Malay	35 (22.2%)
Indian	22 (13.9%)
Disease stage	
I	12 (7.6%)
II	65 (41.1%)
III	49 (31%)
IV	32 (20.3%)
Current chemotherapy	
FEC	147 (93%)
CAF	6 (3.8%)
CMF	5 (3.2%)
Chemotherapy cycles	
1 st cycle	25 (15.8%)
2 nd cycle	30 (25%)
3 rd and more cycle	103 (65.2%)
Educational Level	
Non educated	3 (1.9%)
Primary	21 (13.3%)
Secondary	42 (26.6%)
Diploma	61 (38.5%)
Bachelor	29 (18.4%)
Post graduate	2 (1.3%)

Table 2. Social Characteristics of the Cases

Variable	Value
Anxiety	
Yes	51 (32.3%)
No	107 (67.7%)
History of Motion Sickness	
Yes	13 (8.3%)
No	145 (91.7%)
Social Support	
Yes	115 (73%)
No	43 (27%)
Consumption of Alcohol	
Yes	34 (21.5%)
No	124 (78.5%)
History of Previous Chemotherapy	
In inducing Nausea and/ or Vomiting	
n=133)*	
Nausea Yes	110 (82.6%)
No	23 (17.4%)
Vomiting Yes	99 (74.4%)
No	34 (25.6%)

* 133= They represent those who receive their second, third and more chemotherapy cycles, since they have a history of CINV

acute CINV with delay nausea (n=5; 4.9%) and only 11 (10.8%) did not show any acute CINV nor delay CINV. The Malay patients showed lower incidence of only acute vomiting or nausea as compared with the Chinese. While the incidence of acute CINV among the Indian patients was very rare as compared with the Chinese and Malay patients. These results are clearly shown in Table 3. The majority of the patients showed CINV after their third or more cycles of chemotherapy (n=103; 65.2%), 30 (25%)

Table 3. CINV Characteristics Among Breast Cancer Patients Admitted To Penang Hospital (N=158)

CINV data	Value
(1) Chinese	
Acute+ delayed CINV	45 (44.6%)
Acute nausea+ delayed CINV	12 (11.9%)
No acute+ no delayed CINV	11 (10.9%)
Acute CINV+ delayed vomiting	5 (4.9%)
Acute CINV+ d elayed nausea	5 (4.9%)
Others	23 (22.8%)
(2) Malay	
Delay CINV	9 (25.7%)
Acute nausea+ delayed vomiting	6 (17.1%)
No acute+ no delayed CINV	5 (14.2%)
Delayed vomiting	4 (11.4%)
Others	11 (31.4%)
(3) Indian	
No acute+ no delayed CINV	7 (31.8%)
Only delayed nausea	5 (22.7%)
Avute nausea + delayed nausea	4 (18.2%)
Delayed vomiting	2 (9.1%)
Others	4 (2.5%)
(4) Grades of Acute Nausea	109 (69%)
Grade 1 acute nausea	33 (20.9%)
Grade 2 acute nausea	76 (48.1%)
No acute nausea	49 (31%)
(5) Grades of Delayed Nausea	105 (66.5%)
Grade 1 delay nausea	27 (17.1%)
Grade 2 delay nausea	62 (39.2%)
Grade 3 delay nausea	16 (10.1%)
No delay nausea	53 (33.5%)
(6) Grades of Acute Vomiting	81 (51.3%)
Grade 1 acute vomiting	61 (38.6%)
Grade 2 acute vomiting	18 (15.2%)
Grade 3 acute vomiting	2 (1.3%)
No acute vomiting	77 (44.9%)
(7) Grades of Delay Vomiting	105 (66.4%)
Grade 1 delayed vomiting	42 (22.8%)
Grade 2 delayed vomiting	51 (32.3%)
Grade 3 delayed vomiting	12 (7.6%)
No delay vomiting	53 (37.3%)

after the second cycle, while 25 (15.8 %) after the first cycle of chemotherapy. High percentage of the patients suffered from acute nausea (n=109; 69%), i.e. grade 2 acute nausea (n=76; 48.1%) and grade 1 acute nausea (n=33; 20.9%). A group of the patients (n=49; 31%) did not show any acute nausea. Out of 105 patients (66.5%) who suffered from delayed nausea, (n=27; 17.1%) showed grade 1 delayed nausea, 62 (39.2%) showed grade 2 delay nausea and 16 (10.1%) showed grade 3 delayed nausea phenomena. While 53 (33.5%) of the patients did not show any delayed nausea phenomena. In this study 87(55.1%) patients showed acute vomiting phenomena, whereby 61 (38.6%) of them suffered grade 1 acute vomiting, 18 (15.2%) showed grade 2 acute vomiting and only 2 (1.3%) patients showed grade 3. On the other hand, 77 (44.9%) of the total patients did not show any acute vomiting. Looking at the delayed vomiting phenomena that occurred in 99 (62.7%) patients, the degree of severity varied between patients whereby 36 (22.8%) patients showed

grade 1, 51 (32.3%) grade 2 and 12 (7.6%) showed grade 3, while 59 (37.3 %) patients did not show any.

Statistical analysis

Patient demographic and clinical characteristics were presented descriptively as mean, range, or proportions. Chi-square test was applied to find if there is an association between granisetron with onset and severity of acute and delayed nausea and/ or vomiting. Association between breast cancer patients anxiety, their history of motion sickness with onset and severity of acute and delayed nausea and vomiting. This is to clarify whether phenotype and genotype variant in the three ethnic groups in Malaysia will directly interfere with the clinical action of granisetron in palliating and/ or preventing of acute and/ or delay nausea and vomiting caused by chemotherapy.

The results of Chi-square test showed insignificant association between patients age group with onset and severity of acute and delayed nausea and vomiting since all the P values > 0.05. The P value for the association with the onset is 0.246, with severity of acute nausea is 0.251, with severity of delayed nausea is 0.841, with onset of vomiting is 0.600, with severity of acute vomiting is 0.958 and with severity of delayed vomiting is 0.918). But statistical results showed strong association between patients races with onset and severity of acute and delayed nausea and vomiting since P values for all the results were 0.000. The results also showed insignificant associations between breast cancer stages with onset and severity of acute and delayed nausea and vomiting since the P value with onset of nausea is 0.0322, with severity of acute nausea is 0.786, with severity of delayed nausea is 0.073, with onset of vomiting is 0.493, with severity of acute vomiting is 0.278 and with severity of delayed vomiting is 0.521. The statistical results also showed insignificant association between pre-chemotherapy antiemetic treatment (i.e., granisetron + dexamethasone) with onset of nausea (i.e., acute and delayed nausea) since P > 0.05 (P=0.591). In addition, the results also showed insignificant associations between pre-chemotherapy antiemetic administration with onset of vomiting (i.e., acute and delayed vomiting ; P=0.976), insignificant association between antiemetic treatment pre-chemotherapy with severity of acute nausea (P=0.305), with severity of delayed nausea (P=0.622) and with severity of acute and delayed vomiting (P=0.685; P=0.916). Anxiety also showed insignificant association with onset and severity of acute and delayed nausea and vomiting with P value of 0.629 for onset of nausea, 0.701 for severity of acute nausea, and 0.339 for severity of delayed nausea. The P values for the association with onset of vomiting is 0.452, with acute vomiting is 0.267 and with severity of delayed vomiting is 0.847.

History of motion sickness also showed insignificant association with onset and severity of acute and delayed nausea and vomiting, since P = 0.492 with onset of nausea, 0.368 with severity of acute nausea and 0.826 with severity of delayed nausea. Also it showed insignificant association with onset of vomiting (P= 0.214), severity of acute nausea (P= 0.538) and severity of delayed vomiting (P= 0.097).

Discussion

This is a longitudinal prospective observational study considered as the first study in Malaysia that is looking for the effect of variant phenotypical and genotypical of the three ethnic Malaysian races on the clinical action of granisetron. The main results of this study shows that Chinese is the main race who suffered from breast cancer here followed by the Malays then Indians. According to the National Cancer Registry of Malaysia (2003) the incidence of cancer is highest among the Chinese as compared to the Malay and Indian (National Cancer Registry of Malaysia, 2003).

This result of high cancer incidence among the Chinese followed by the Malay and the Indian was also observed by Kaur et al., (2007) whereby breast cancer in Penang occur mostly among the Chinese (62.5%) followed by the Malays (26.7%) and the Indians (10.2%). Kaur et al (2007) related their findings to the local racial population since Chinese was the major race group in Penang. This could also explain the results whereby the Chinese was the highest ethnic group experiencing nausea and vomiting as compared to the Malays and finally the Indians (Kaur et al., 2007). Majority of these breast cancer patients who suffered from and developed nausea and vomiting were between 50-59 years of age. According to the National Cancer Registry of Malaysia (2003), breast cancer is more predominant at age of 50 years or more (National Cancer Registry of Malaysia, 2003). One hundred and forty seven (93%) patients were treated with FEC regimen which is the optimal anthracycline-containing combinations and at present remain a choice for patients with breast cancer. Many trials have shown that the incidence of febrile neutropenia with FEC is lower than the 20% threshold for primary G-CSF prophylaxis stipulated by the international guidelines (Fumoleau et al., 2003; Verrill, 2009).

As is clear from the results of this present study, the Chinese appear to be the most vulnerable race in controlling nausea and vomiting (acute and delayed form). While the Malay and the Indian both appeared to be more resistant than the Chinese especially the Indian since they showed the least incidence of nausea and vomiting (acute and delayed). Nausea and vomiting occurred despite the pre chemotherapy antiemetic treatment with granisetron and dexamethasone to all the three races. According to Rais et al., (2006) genetic polymorphism is the major reason of variation in the metabolism of different drugs and environmental chemicals (Rais et al., 2006). Numerous alleles of CYP3A4 have been reported and since the CYP3A4 is the main enzyme responsible for granisetron metabolism any genetic differentiation between these three races will effect the granisetron metabolism and availability inside the body (Rais et al., 2006). Huang et al., 2003 indicated that CYP3A4 enzyme production and activity is highly increased in Chinese breast cancer patients especially those who have positive lymph node spread. As in our study all the Chinese patients showed positive lymph node spread thus this could cause an increases metabolism of granisetron leading to decrease in its bioavailability in their blood and causing them to experience acute nausea and/ or vomiting. This will also

explain the high incidence of delayed nausea and vomiting since weak control of the acute nausea and vomiting will cause difficulty in controlling delayed phase (Hesketh, 2005). Rubenstein reported that women treated with moderately emetogenic chemotherapy just like in our study showed poor response to 5-HT₃ used alone or in combination with dexamethasone for complete protection of acute CINV (Rubenstein, 2005).

According to the result of Ruzilawati et al., (2007) the presence of mutation within CYP3A4*18 allele among the Malay population in Malaysia, will have an impact on the metabolism of different drugs by CYP3A4 enzyme. Ruzilawati et al., (2007) reported the presence of a mutation within CYP3A4*18 allele among the Malay population in Malaysia. This mutation with CYP3A4*18 allele will lead to decrease in the activity of the CYP3A4 enzyme hence will have an impact on the metabolism of different drugs. Hence reduced metabolism of granisetron might occur among the Malay patients resulting in having better control of the acute and delayed nausea and vomiting. However this might not happen among Chinese since Hsieh and his colleague mentioned that the incidence of mutation within alleles (CYP3A4*4, CYP3A4*5 and CYP3A4*6) which lead to decrease in CYP3A4 enzyme activity is very rare in the Chinese races (Hsieh et al., 2001). Besides that according to Yi-Fan et al., (2003) Chinese might metabolized and eliminate Loratadine faster than the Caucasian due to higher pharmacokinetic activities. In addition it was advice that loratadine should be given for two times per day to the Chinese in order to get the same clinical effect as the Caucasian. Hence these reports could help to explain the results obtained in our study whereby the chemotherapy induced nausea and vomiting is more seen in the Chinese than the Malay.

In this study the Indian race demonstrate a much better control for chemotherapy induced acute and delayed nausea and/ or vomiting. The main explanation for this is based on the study by Rais et al., (2006) that demonstrated the absence of common CYP3A4 genotypes in Northern Indians. They also indicated that CYP3A4*2, *4, *5, *6 and *10 alleles which are commonly found in other ethnics are absent in the Indian (Rais et al., 2006). Thus the absence of CYP3A4 enzyme among the Indian will have an impact on the therapeutic outcome as well as toxicity of the substrate drugs such as granisetron since it is mainly metabolized by CYP3A4 enzyme. The absence of this enzyme will cause the concentration of granisetron in the blood to remain high and this resulted in a good control of chemotherapy induced acute nausea and/ or vomiting. Even though granisetron was given in combination with dexamethasone to enhance the action of 5-HT₃ receptor antagonist but according to the study by Dempsey and his colleague, dexamethasone did not influence total CINV control in the granisetron group (Dempsey et al., 2010).

According to the results of our study, the delayed CINV incidence is higher in the Chinese race then the others two races. The main reason would be the poor control of metoclopramide plus dexamethasone tablets used to control delayed phase. This point has been pointed out by Molassiotis et al., 2002 who indicated that the antiemetic effect of metoclopramide plus dexamethasone

Bassam Abdul Rasool Hassan and Zuraidah Binti Mohd Yusoff against delayed nausea and vomiting is unsatisfactory. Besides that Molassiotis and his colleague mentioned that there is an association between acute CINV and delayed CINV, so the failure in control acute nausea and vomiting will lead to fail in controlling the delayed one too (Molassiotis et al., 2002).

As seen in Table 3, there are some Chinese patients who did not show any acute or delayed nausea and/ or vomiting. This may be explained in more than one way i.e., firstly they received lower doses of cyclophosphamide (700-800 mg) and 5-fluorouracil (700-800 mg) as compared to those with CINV phenomena who were on cyclophosphamide (900-1200 mg) and 5-fluorouracil (900-1200 mg). According to Hesketh, chemotherapy doses do play a major role in the incidence of nausea and vomiting (Hesketh, 2005). While the second explanation could be due to ethnic variation. As reported by Gross et al., 1999 and written in Wikipedia the free encyclopedia, the Han represents the majority of the Chinese race. The Han consists of many subgroups (Wu, Xiang, Min, Hakka, Gan, Tanka, Peranakans, Chuanqing, Kwongsai, Yue, etc) and there are substantial genetic, linguistic, cultural, and social diversity among them. This diversity principally caused by thousands of years of immigration and assimilation of various regional ethnicities (Gross, 1999; Wikipedia the Free Encyclopedia, 2010). The Chinese who migrate to Malaysia included the Hakka, Teochew, Fuchow, Hainanese, Cantonese and Hokkein (Mokhlis, 2009). These diversities within the Chinese themselves indicated that they may have different phenotype, pharmacokinetic and genotype that lead to these variant events. So these might explain the reason that some of the Chinese did not show any acute and/ or delay CINV.

Majority of the patients who suffered from CINV were receiving their third chemotherapy cycle followed by those who were receiving their 2nd cycle then lastly those who received their first cycle. The main explanation for that, according to Cohen and his colleague, patients who experienced CINV whether acute and/ or delayed at their 3rd or more cycles, must be suffering from CINV in their previous cycles i.e., 1st or 2nd cycle. So when the patients develop CINV after their first cycle there would be a great chance for them to develop CINV after their subsequent cycles (Cohen et al., 2007).

This point has been confirmed depending on the results of our presented study (Table 2) that showed the majority of patients (n=110; 82.6%) who received their second, third and more of chemotherapy cycles (n=133) do have a history of incidence of nausea and/ or vomiting with previous cycles of chemotherapy.

Also the occurrence of severe acute and delayed nausea and vomiting observed in our study is due to the low effect or control of the antiemetic treatments and not because of cancer stages. It is known that patients who suffered from early stages of breast cancer have a better performance status than those who suffered from advanced breast cancer stages (Booth et al., 2007). This point has been shown in our present study since the statistical results showed insignificant association between breast cancer stages with onset and severity of acute and delayed nausea and vomiting.

Moreover the results of our presented study (Table 2) showed that the minority of the breast cancer patients suffered from anxiety (n=51; 32.3%) with a non-significant association with onset and severity of acute and delayed nausea since all the *P* values were > 0.05.

The main explanation for this low incidence of anxiety and the insignificant association with onset and severity of acute and delayed nausea and vomiting is because of the presence of social support which will lead to lowering of patients anxiety, especially in case of breast cancer patients when they have a social support as in our presented study their anxiety will be low, which has been proven clinically (Naing et al., 2010). Moreover Naing and his colleague mentioned that when patients have lower than 9 years of education i.e., low education level, they will show more psychologically distressed and depressive symptoms than the highly educated ones. As it is clear in Table 2 of this presented study the majority of the patients were having education for more than 9 years i.e., consider as highly educated. So this could also explain the low incidence of anxiety with our patients.

Also there was no significant association observed between motion sickness with onset and severity of acute and delayed nausea and vomiting. Also only a small proportion (n=34; 21.5%) of the breast cancer patients studied consumed alcohol. All these data are shown in Tables 1 and 2.

Based on the present findings, genetic polymorphisms in the three races in Malaysia significantly effect the granisetron clinical antiemetic action, and could be considered as the only risk factor which plays role in incidence of nausea and vomiting. We conclude that Chinese patients with breast cancer should be treated with a different type of 5-HT₃ receptor antagonist such as tropisetron and dolasetron, since they are predominantly metabolized by CYP2D6 only. Bernard et al., 2006 reported that a high proportion as much as 50% of the Asian population has the CYP2D6*10 allele. This allele is responsible for reducing the activity of CYP2D6 enzyme within the Chinese and other Asian and make them intermediate metabolizers (IM). This IM phenotype has a wide spectrum of metabolic activity from poor metabolizers (PM) to ultra rapid metabolizers (UM). So the IM will get the best clinical activities of the administrated drug i.e., 5-HT₃ receptor antagonist to prevent nausea and/ or vomiting in cancer patients who were treated with chemotherapy (Bernard et al., 2006).

Acknowledgments

We like to thank all the hospital staff for their cooperation and their efforts to help us for doing this study. Also we like to thank all the staff in the oncology clinic and the record office of the hospital for their efforts by helping us to get the patients files.

References

Apró M (2004). Granisetron: an update on its clinical use in the management of nausea and vomiting. *Oncologist*, **9**, 673-80.

- Bernard S, Neville KA, Nguyen AT, et al (2006). Interethnic differences in genetic polymorphisms of CYP2D6 in the U.S. population: clinical implications. *Oncologist*, **11**, 126-35.
- Bloechl-Daum B, Deuson RR, Mavros P, et al (2006). Delayed nausea and vomiting continue to reduce patients' quality of life after highly and moderately emetogenic chemotherapy despite antiemetic treatment. *J Clin Oncol*, **24**, 4472-8.
- Booth CM, Clemons M, Dranitsaris G, et al (2007). Chemotherapy-induced nausea and vomiting in breast cancer patients: a prospective observational study. *J Support Oncol*, **5**, 374-80.
- Cohen L, De Moor CA, Eisenberg P, et al (2007). Chemotherapy-induced nausea and vomiting-incidence and impact on patient quality of life at community oncology settings. *Support Care Cancer*, **15**, 497-503.
- Dempsey CL, Coop AJ, Shillington A, et al (2010). Antiemetic effectiveness of ondansetron and granisetron in: results. In: http://www.medscape.com/viewarticle/475180_3, ed. (Accessed 2010).
- Dupont WD, Plummer WD (2004) PS: Power and Sample Size Calculation IN BIostatISTICS, V. (ed. Power sample size). 2.1.31 ed. Nashville, Vanderbilt Biostatistics (Accessed 2004).
- Fumoleau P, Bonnetterre J, Luporsi E (2003). Adjuvant chemotherapy for node-positive breast cancer patients: which is the reference today? *J Clin Oncol*, **21**, 1190-2.
- Gross SA, Bridge S, Shenfield GM (1999). Pharmacokinetic of tolbutamide in ethnic Chinese. *J Clin Pharmacol*, **47**, 151-6.
- Hesketh PJ (2005). Management of nausea and vomiting in cancer treatment: introduction, scope of the problem. In: Hesketh PJ, ed. Management of nausea and vomiting in cancer and cancer treatment. Jones and Bartlett, Mississauga, 1-14.
- Hsieh KP, Lin YY, Cheng CL, et al (2001). Novel mutations of CYP3A4 in Chinese. *Drug Metab Dispos*, **29**, 268-73.
- Huang P, Zhu B, Wang LS, et al (2003). Relationship between CYP3A activity and breast cancer susceptibility in Chinese Han women. *Eur J Clin Pharmacol*, **59**, 471-6.
- Kaur G, Rosli Ismail Lee, Suk Kam, et al (2007). Assessment of correlation between clinicopathological features and lymph node metastases in breast cancer. *Internet J Pathol*, **5**, 1528-8307.
- Kaiser R, Sezer O, Papies A, et al (2002). Patient-tailored antiemetic treatment with 5-Hydroxytryptamine type 3 receptor antagonists according to cytochrome P-450 2D6 genotypes. *J Clin Oncol*, **20**, 2805-11.
- Mokhlis S (2009). Malaysian Chinese consumers: their ethnic attitudes and shopping orientations. *Int J Business and Management Services*, **4**, 53-62.
- Molassiotis A, Mok TS, Yam BM, et al (2002). An analysis of the antiemetic protection of metoclopramide plus dexamethasone in Chinese patients receiving moderately high emetogenic chemotherapy. *Eur J Cancer Care*, **11**, 108-13.
- Naing KNJ, Azillah AAN, Nooriny I, et al (2010). Anxiety and depressive symptoms and coping strategies in nasopharyngeal carcinoma patients in hospital Kuala Lumpur. *Malaysian J Med Hlth Sci*, **6**, 71-81.
- National Cancer Registry of Malaysia (2003). Second report of the national cancer registry cancer incidence in Malaysia 2003. In: Malaysia, Ministry of Health (ed., National Cancer Registry) (Accessed 2003).
- Rais N, Chawla YK, Kohli KK (2006). CYP3A phenotypes and genotypes in north Indians. *Eur J Clin Pharmacol*, **62**, 417-22.
- Ruzilawati AB, Mohd Suhaimi AW, Gan SH (2007). Genetic polymorphisms of CYP3A4: CYP3A4*18 allele is found in five healthy Malaysian subjects. *Clin Chim Acta*, **383**, 158-62.
- Rubenstein E (2005). The role of prognostic factors in chemotherapy induced nausea and vomiting. In: Hesketh PJ, ed. Management of Nausea and Vomiting in Cancer and Cancer Treatment. Jones and Bartlett Publishers, Mississauga, 87-98.
- Verrill M (2009). Chemotherapy for early-stage breast cancer: a brief history. *Br J Cancer*, **101**, 2-5.
- Yang YS, Wong LP, Lee TC, et al (2004). Genetic polymorphism of cytochrome P450 2C19 in healthy Malaysian subjects. *Br J Clin Pharmacol*, **58**, 332-5.
- Yi-Fan Z, Xiao-Yan C, Da-Fang Z, et al (2003). Pharmacokinetics of loratadine and its active metabolite descarboethoxyloratadine in healthy Chinese subjects. *Acta Pharmacol Sin*, **24**, 715-8.
- Wikipedia the Free Encyclopedia (2010). Han Chinese. In: Wikipedia the Free Encyclopedia, ed. Wikipedia the free encyclopedia. (Accessed 2010).