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Pharmacogenetics of antiemetics in Indonesian cancer patients

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Pharmacogenetics of Antiemetics in Indonesian Cancer Patients

Dyah Aryani Perwitasari

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Pharmacogenetics of Antiemetics in Indonesian Cancer Patients

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Contents

Chapter 1	General introduction	**7**
Chapter 2	Antiemetic drugs in oncology: pharmacology and individualization by pharmacogenetics	**17**
Chapter 3	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	**39**
Chapter 4	Differences in 5-Hydroxytryptamine-3B haplotype frequencies between Asians and Caucasians	**57**
Chapter 5	Translation and validation of EORTC QLQ-C30 into Indonesian version for cancer patients in Indonesia	**67**
Chapter 6	Impact of chemotherapy induced nausea and vomiting on quality of life in Indonesian patients with gynecological cancer	**89**
Chapter 7	General discussion and future perspectives	**105**
Chapter 8	Summary	**115**
Chapter 9	Rangkuman (Summary in Indonesian)	**119**
Chapter 10	Samenvatting (Summary in Dutch)	**123**
	About the author	**129**
	Acknowledgements	**133**

1

General introduction

INTRODUCTION

Cancer is the seventh leading cause of death in Indonesia, after death from trauma, perinatal and diabetes mellitus.[1] More specifically, the number of new female cancer cases was 156.500 in 2006.[2] The most frequent female cancer in Indonesia is breast cancer, while the incidence of gynecologic cancer is 19%.[2] This number is decreasing, as in 2002 cervical cancer still showed the highest incidence of female cancer in Indonesia[3] and this may be the result of the Indonesian government collaboration program aimed to prevent the widespread of gynecologic cancer and to improve its treatment.[4]

For gynecologic cancer patients diagnosed with advanced stage of disease, chemotherapy, with or without radiotherapy, are the treatment of choice. Although this treatment has no curative intent, chemotherapy does increase progression-free survival and overall survival time.[5,6] Platinum agents are the mainstay of treatment of cervical cancer both in the palliative, adjuvant and neo adjuvant setting.[6-9] However, the use of platinum containing chemotherapy is accompanied by serious side effects and this is the main reason for dose-reductions and preliminary termination of therapy. Indeed, in a study of cisplatin toxicity in 400 patients who received high dose of cisplatin weekly, it was found that 26.5% patients did not complete the cycles because of cisplatin toxicity. The major toxicitiy of cisplatin was nausea and vomiting, whereas ototoxicity, neurotoxicity, hematologic toxicity and nephrotoxicity occurred in 1-10% patients who did not complete the full cycles of chemotherapy.[7] Nausea and vomiting, ototoxicity, neurotoxicity, hematologic toxicity and nephrotoxicity were present in 40%, 81%, 40%, 30% and 40% of the patients, respectively.[7,8]

Cisplatin is a cytotoxic agent known for its emetogenic potential: more than 90% patients treated with cisplatin and without antiemetic treatment experience chemotherapy-induced nausea and vomiting (CINV).[9-11] CINV is one of the most distressing side effects[12,13] and prevention of CINV is the main goal of antiemetic treatment in patients receiving highly or moderately emetogenic cytostatic treatment.[14] However, in a study on granisetron efficacy in patients treated with highly emetogenic chemotherapy, around 20-50% showed the delay of treatment because of CINV.

CINV is categorized into 5 groups: acute, delayed, refractory, breakthrough and anticipatory CINV. Acute CINV occurs within 24 hours after chemotherapy and delayed CINV occurs 24 or more hours after chemotherapy administration and persists until 5 days. Anticipatory chemotherapy can be present before, during and following chemotherapy and is related to poor control of emesis in previous chemotherapy cycles. Some of the stimulants such as taste, odor, perception and anxiety can trigger anticipatory

nausea and vomiting. Patients experiencing breakthrough CINV need rescue antiemetic medication despite the use of prophylactic antiemetic treatment. Refractory CINV can occur if patients did not have complete control of nausea and vomiting in previous cycles and experience CINV in the subsequent cycle.[16,18] Poor control of acute CINV can increase the presence of delayed CINV and potentially impacts patients' Quality of Life (QoL).[16,19,20]

In the recent years, the insight in the pathophysiology of CINV has improved considerably and it is shown that neurotransmitters play an important role in the pathogenesis of CINV.[15] Dopamine, serotonin and substance P are thought to be the main neurotransmitters involved in CINV. Serotonin, substance P and their receptors are located in the gastrointestinal tract as well as in the central nervous system. As a response to chemotherapeutic agents (or their metabolites), these neurotransmitters are released in the gastrointestinal tract or in the medulla oblongata. The stimulation by neurotransmitter subsequently produces impulses that are sent to the vomiting centre causing nausea and vomiting.[15,16] In addition to serotonin and substance P, other neurotransmitters such as cannabioids, histamine, dopamine, acethylcholine and γ-Amminobutyric-Acid (GABA) are thought to play a role in the nausea and vomiting reflex. It is assumed that in total more than twenty neurotransmitters and receptor systems contribute to the vomiting reflex, nevertheless the precise mechanisms have not yet been clarified.[15]

Consequently, nausea and vomiting can be pharmacologically treated and prevented by agents which block the receptors of these neurotransmitters, such as dopamine receptor antagonists, 5-hydroxytriptamine 3 (5-HT3) receptor antagonists and neurokinin 1 (NK1) receptor antagonists. The introduction of 5-HT3 receptor antagonists more than 20 years ago was an important step forward in the prevention and treatment of CINV. The use of these drugs in patients treated with highly emetogenic chemotherapeutic drugs results in a 60-75% response rate with regard to control of CINV and the combination of these agents with a corticosteroid further improves response rates to 75-85%.[15,17,18] Currently, the use of aprepitant, NK1 antagonist, 5-HT3 receptor antagonists and dexamethasone could increase the complete protection of acute emesis by another 10-15% in cancer patients.[7,19] Despite these important improvements in the treatment and prevention of CINV, still 20% of the patients can not be treated adequately.

The inter-individual variation in response to antiemetic drugs is related to patient and treatment characteristics such us age, gender, history of motion sickness, history of morning sickness and history of alcohol drinking.[9,19] In addition, some pharmacogenetic studies found a role for heritable variants in the *ABCB1* (ATB Binding Casette Subfamily B Member

1) gene, *OCT1* (Organic Cation Transporter 1) gene, *5-HT3* receptor gene and *CYP2D6* gene in explaining variation in response to antiemetics in oncology.[20-25] All of these genes encode proteins and enzymes involved in the pharmacokinetics or pharmacodynamics of antiemetic drugs.

Drug transporters play an important role in pharmacokinetics especially in drug absorption in the gastrointestinal tract and drug disposition f.e. passage of drugs across the blood–brain barrier.[26] The transporter ABCB1 has a role in the pharmacokinetics of ondansetron. Indeed, in vitro experiments showed that inhibition of ABCB1 resulted in a decrease of transepithelial transport of ondansetron.[27] In a clinical study with the the 5-HT3 receptor antagonists granisetron, tropisetron and ondansetron in cancer patients treated with moderately or highly emetogenic chemotherapy, the C3435T variant in the *ABCB1* was associated with antiemetic response. The patients with the TT genotype showed a 40% higher response rate than the carriers of the C allele.[20] It is thought that the polymorphism in *ABCB1* influences passage and thus the availability of ondansetron across the blood brain barrier and gastrointestinal tract.

The 5-HT3 receptor is a ligand-gated ion channel with 5 subunits (A,B,C,D and E)[28] and for the pharmacological function of the 5-HT3A and 5-HT3A/B receptors the 5-HT3B subunit plays a predominant role.[29] Polymorphisms in the genes encoding the 5-HT3A and 5-HT3B receptors may influence the receptor function.[30] In the study in cancer patients, variants in the gene encoding the 5-HT3A receptor did not show a relationship with response to 5-HT3 receptor antagonists[24] but such a relationship was shown for genetic variants encoding the 5-HT3B and 5-HT3C receptor[21,31] and also a polymorphism in the 5-HT3D receptor could contribute to the individualized response of 5-HT3 receptor antagonists.[22]

Drug-metabolizing enzymes have an important role in the pharmacokinetics of drugs as well.[26] All of the 5-HT3 receptor antagonists are metabolized by the hepatic CYP2D6 family, though in the different proportions.[16] Ultrarapid metabolizing patients with a duplication of a CYP2D6 allele showed a decrease of ondansetron efficacy, because the rapid inactivation of the drug.[32,33] Based on the CYP2D6 phenotypes, Ultrarapid Metabolizers (UM) indeed showed more severe nausea and vomiting as compared to patients with the Extensive Metabolizers (EM) phenotype.[23]

Metoclopramide as a dopamine antagonist is the most common used of antiemetic drug after chemotherapy treatment in Indonesia. The passage of metoclopramide across the blood–brain barrier is influenced by ABCB1 transporter. This model was shown by the knock-out mouse which showed that the presence of P-glycoprotein could decrease the

metoclopramide concentrations in the brain.[34] In case of its metabolism, metoclopramide is primarily metabolized by CYP2D6.[35] The previous report in two cancer patients presented that metoclopramide could induce extrapyramidal syndrome in patients with inactive alleles of CYP2D6.[36]

In summary, despite the availability of effective antiemetic drugs for the treatment and prevention of nausea and vomiting in cancer patients treated with highly emetogenic chemotherapeutic drugs, their use is far from optimal.

Nausea and vomiting still occurs in a considerable number of patients and potentially impacts both outcome of chemotherapeutic treatment and the patients' quality of life.[12,37,38] Indeed, some studies showed impact of poor control of CINV on QoL in cancer patients[12,37,38] but these effects have never been studied in Indonesian cancer patients. One reason for this is the lack of a valid and reliable QoL instrument to assess the QoL of Indonesian cancer patients.

In addition, some studies have suggested predictability of response to antiemetic treatment in cancer patients[20,21,23,25,31,38,39] which could be an effective way to further individualize and improve prevention of CINV. However, these studies were carried out in Caucasian cancer patients and similar studies in Indonesian cancer patients have not yet been performed. Pharmacogenetic findings can not always be simply translated among ethnicities due to differences in allele frequencies, haplotypes and gene functionality.

AIMS AND SCOPE

The general aim of this thesis is to optimize the prevention and treatment of CINV by exploration of pharmacogenetic biomarkers and to determine the impact of CINV of QoL in Indonesian cancer patients.

Chapter 2 describes the fundamentals and clinical pharmacology including the pharmacogenetics of antiemetic drugs applied in oncology. It will clarify the mechanisms of action of antiemetic drugs in preventing acute and delayed CINV. In addition, pharmacogenetic studies on 5-HT3 receptor antagonists related to the *ABCB1* gene, *5-HT3* receptors gene and *CYP2D6* will be presented as well.

In the next chapter, the results of a clinical pharmacogenetic study investigating the association of variants in the genes encoding ABCB1, the 5-HT3B receptor and CYP2D6 with CINV in patients with cancer in Indonesia are presented (Chapter 3). In Chapter 4 we compared haplotype frequencies of variants in the gene encoding the 5-HT3B receptor

between Indonesians and Caucasians as too explore a source for ethnic differences in response to 5-HT3 receptor antagonists.

Chapter 5 of this thesis provides the results of a study on the translation and validation of the EORTC QLQ-C30 in the Indonesian language. The aim of this chapter is to provide a valid instrument which can be used to measure patients' quality of life. We applied the Indonesian version of the EORTC QLQ-C30 in Indonesian gynecologic cancer patients as to assess the impact of chemotherapy on QoL and compared QoL at baseline and 5 days after chemotherapy (Chapter 6). The Indonesian version of EORTC QLQ-C30 and SF-36 questionnaires are used in this chapter to measure the patients' daily functions, such as: physical, emotional, role, emotional, general QoL, and symptoms related cancer or cancer treatment.

A general discussion is presented in Chapter 7, and Summaries in English and Indonesian are given in Chapters 8 and 9 respectively.

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2

Antiemetic drugs in oncology: pharmacology and individualization by pharmacogenetics

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ABSTRACT

Objective: Nausea and vomiting are the most distressful side effects of cytotoxic drugs in cancer patients. Antiemetics are commonly used to reduce these side effects. However, the current antiemetic efficacy is about 70%-80% in patients treated with highly-emetogenic cytotoxic drugs. One of the potential factors explaining this suboptimal response is variability in genes encoding enzymes and proteins which play a role in metabolism, transport and receptors related to antiemetic drugs. Aim of this review was to describe the pharmacology and pharmacogenetic concepts of antiemetics in oncology.

Method: Pharmacogenetic and pharmacology studies of antiemetic in oncology published between January 1997 to February 2010 were searched in PubMed. Furthermore, related textbooks were also used for exploring the pharmacology of antiemetic drugs. The antiemetic drugs which were searched were the 5-hydroxytryptamine 3 receptor antagonists (5-HT3RAs), dopamine antagonists, corticosteroids, benzodiazepines, cannabinoids, antihistamines and neurokinin-1 antagonists.

Results: The 5-HT3RAs are widely use in highly emetogenic chemotherapy in combination with dexamethasone and neurokinin-1 antagonist, especially in acute phase. However, the dopamine antagonists and benzodiazepines were found more appropriate for use in breakthrough and anticipatory symptoms or in preventing the delayed phase of chemotherapy-induced nausea vomiting. The use of cannabinoids and antihistamines need further investigation. Only six articles on pharmacogenetic of the 5-HT3RAs in highly emetogenic chemotherapy are published. Specifically, these studies investigated the association of the efficacy of 5-HT3RAs and variants in *multi drug resistence 1* (*MDR1*) gene, *5-HT3A*, *B* and *C* receptor genes and *CYP2D6* gene. The pharmacogenetic studies of the other antiemetics were not found in this review.

Conclusion: It is concluded that pharmacogenetic studies with antiemetics are sparse. It is too early to implement results of pharmacogenetic association studies of antiemetic drugs in clinical practice: confirmation of early findings is required.

INTRODUCTION

Chemotherapy Induced Nausea and Vomiting (CINV) are the most distressing side effects in cancer patients treated with chemotherapy and can have a negative impact on the patients' quality of life.[1] Moreover, CINV can seriously influence patients' adherence to chemotherapy[2] and may thus influence progression free survival and overall survival. In the past, before using standard antiemetic drug regimens, nausea and vomiting resulted in up to 20% of patients in delay or refusal of chemotherapy.[3] Highly effective antiemetic drugs are available nowadays and their standardized use increases patients' quality of life.[4] However, in patients receiving highly-emetogenic cytotoxic drug therapy the proportion of patients experiencing effective antiemetic therapy is only 70%-80%.[5] One of the factors responsible for variable response to antiemetic drugs is the inter-individual difference in biotransformation. Moreover, polymorphisms in genes encoding drug receptors related to the antiemetic drugs along with other patient related risk factors such as gender, age, and drug related factors such as emetogenic potential of chemotherapy may explain inter-individual differences in antiemetic drug response.[6]

OBJECTIVE

The aim of this paper is to review the mechanism of action and pharmacology and the potential role of pharmacogenetics of antiemetic drugs in oncology.

METHODS

Studies on the pharmacology and pharmacogenetics of the 5-hydroxytryptamine 3 receptor antagonists (5-HT3RAs), dopamine antagonists, corticosteroids, benzodiazepines, cannabinoids, antihistamines and neurokinin-1 antagonists were searched in PubMed January 1997 to February 2010. In addition, pharmacology textbooks were also reviewed to summarize the mechanism and pharmacological effects of antiemetics.

RESULTS

Pharmacogenetic studies of antiemetics in oncology are scarce and the individual studies are relatively small: in four studies more than 200 patients, in one study 120 patients and in one study 70 patients were included. These studies investigated the pharmacogenetics

of 5-HT3RAs in *Multi Drug Resistence1* (*MDR1*) gene, *5-HT3 A*, *B* and *C* receptor genes and the *CYP2D6* gene. The summary of these studies is listed in Table 2.1.

Furthermore, more articles related with mechanism and pharmacologic effects were found in this review. The mechanisms of antiemetics are listed in Figure 2.1. The mechanism and pharmacology effect of antiemetics will be discussed below.

Table 2.1 Pharmacogenetic studies of antiemetics

Drugs target (author, year of publication)	Gene	Endpoint	N	Results
Ondansetron or tropisetron Kaiser et al. (2002)[20]	*CYP2D6*	Nausea and vomiting on highly emetogenic cytotoxic drug	270	UMs demonstrate the highest incidence and severity of nausea and vomiting. Frequency of UMs was 1.5%.
Ondansetron or tropisetron Tremblay et al. (2003)[52]	*5-HT3B receptor*	Nausea and vomiting on high emetogenic cytotoxic drug	286	*5-HT3B* receptor gene may serve as genetic predictor for antiemetic therapy with the deletion AAG variant (OR = 32) after adjusted with other risk factors of emesis.
Tropisetron Kaiser et al. (2004)[6]	*5-HT3A receptor*	Nausea and vomiting on high emetogenic cytotoxic drug	242	There were 21 polymorphisms in *5-HT3A* receptor gene, whereas the 15 polymorphisms had partial linkage each of them. The haplotypes in these genes did not have significant association with chemotherapy induced nausea and vomiting.
Tropisetron, granisetron, ondansetron. Babaoglu et al. (2005)[57]	*ABCB 1 (MDR 1)*	Nausea and vomiting on high emetogenic cytotoxic drug	216	The complete control rate of nausea and vomiting was higher in subjects with ABCB1 TT genotype as compared with those with TC or CC genotype (92.9% v 56.1% v 47.6%, $P = 0.044$)
Ondansetron Fasching et al. (2008)[54]	*5-HT3C receptor*	Nausea and vomiting on moderate emetogenic cytotoxic drug	120	Variant genotype of K163N was associated with vomiting (RR = 2.62)
Dolasetron or tropisetron Ward et al. (2008)[53]	*5-HT3C receptor*	Nausea and vomiting on high emetogenic cytotoxic drug	70	*5-HT3C* receptor gene may not serve as genetic predictor for antiemetic therapy

Ums, Ultra-rapid metabolizers; *5-HT3A*, *5-Hydroxytriptamine 3A*; *5-HT3B*, *5-Hydroxytriptamine 3B*; *5-HT3C*, *5-Hydroxytriptamine 3C*; *ABCB1*, *ATP Binding Casette*, *subfamily B*, *member 1*; *MDR1*, *Multi-Drug Resistence 1*.

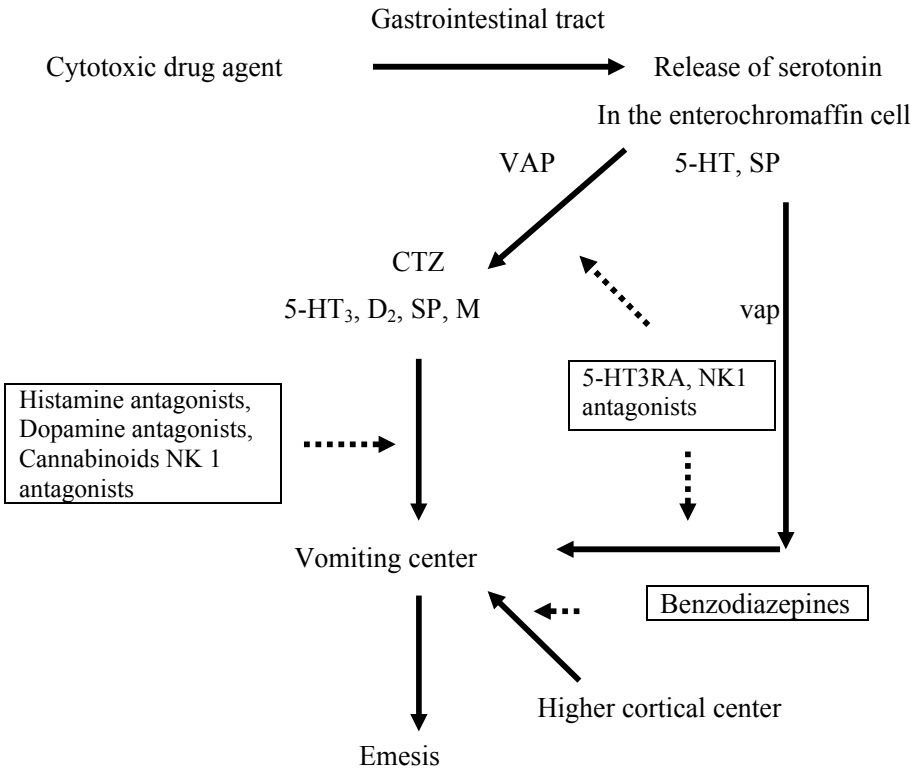

Figure 2.1 Activation of emetic pathway by cytotoxic drugs and site of action of ant-emetic drugs. Adapted from [10, 26, 58]. 5-HT, 5 Hydroxytriptamin; D_2, dopamine; SP, substance P; H, histamine; M, muscarinic; CTZ, chemoreceptor trigger zone; VAP, vagal afferent pathway; 5-HT3RA, 5-HT3 receptor antagonist. Emesis pathway *solid arrow*. Sites of action of drugs *dotted arrow*.

DISCUSSION

Chemotherapy Induced Nausea and Vomiting (CINV)

Based on the emetogenic potential, cytotoxic drugs are classified into several categories: 1) highly-emetogenic, which can cause symptoms in > 90% patients without antiemetic drug treatment, 2) moderate risk, which can cause symptoms in 30%-90% of patients 3) low risk with 10%-30% of symptomatic patients and 4) minimally emetogenic with < 10% of symptomatic patients. Table 2.2 lists the emetogenic categories for various chemotherapeutic agents.[7]

Table 2.2 Emetogenicity of chemotherapeutic agents (Adapted from [7])

Emetogenic potential	Cytotoxic drug	Dosage
High	Cisplatin	
	Cyclophosphamide	> 1,500 mg/m^2
	Dacarbazine	
	Mechloretamine	
	Carmustine	
	Streptozotocin	
Moderate	Cyclophosphamide	< 1,500 mg/m^2
	Carboplatin	
	Doxorubicin	
	Cytarabine	> 1,000 mg/m^2
	Oxaliplatin	
	Ifosfamide	
	Daunorubicin	
	Epirubicin	
	Idarubicin	
	Irinotecan	
Low	Paclitaxel	
	Docetaxel	
	Mitoxantrone	
	Topotecan	
	Etoposide	
	Pemetrexed	
	Methotrexate	
	Mitomycin	
	Gemcitabine	> 1,000 mg/m^2
	Cytarabine	
	5-Fluorouracil	
	Bortezomib	
	Cetuximab	
	Trastuzumab	
Minimal	Bleomycin	
	Busulfan	
	2-Chlorodeoxyadenosine	
	Fludarabine	
	Vinblastine	
	Vincristine	
	Vinorelbine	
	Bevacizumab	

Emetogenicity includes both onset and duration of nausea and vomiting.[2] In patients receiving a combination of cytotoxic drugs, the classification of emetogenicity is based on the cytotoxic drug with the greatest emetogenic potential.[8] Specifically, for defining the emetogenicity of combination regimens of cytotoxic drugs which required a more intensive antiemetic prophylaxis and therapy, the following situations may occur: 1) the

minimal emetogenic agent does not contribute to the emetogenicity of the combined regimen, 2) the low emetogenic agents will increase the emetogenicity of the combined regimen by one level greater than the most emetogenic agent in the regimen, 3) the moderately and highly emetogenic agents will increase the emetogenicity of each drug in the combined regimen by one level,[9] e.g. combination of doxorubicin and cyclophosphamide are highly emetogenic, although both drugs alone are classified as moderate.

CINV is categorized as acute (occurring within 24 hours of therapy), delayed (persisting for 6-7 days after therapy) or anticipatory (occurring prior to chemotherapy administration). Breakthrough nausea and vomiting refer to uncontrollable symptoms and need rescue antiemetics despite the use of prophylactic antiemetics. Some patients also experience refractory nausea and vomiting when they did not receive adequate control of nausea and vomiting in prior cycles.[2]

Cytotoxic drugs can cause emesis through stimulation in the neuron-anatomical centers: 1) the emetic center, 2) the area postrema or chemoreceptor trigger zone (CTZ), and 3) the vagal nerve afferents.[10] The CTZ is sensitive to chemical stimuli, and is the main site of action of antiemetic drugs.[11] However, the blood-brain barrier which is closely located to the CTZ is permeable allowing circulating mediators to act directly to the emetic center.[11] However, newer insight from animal studies suggests that an anatomically discrete vomiting center is unlikely to exist. Rather, a number of loosely organized neuronal areas within the medulla probably interact to coordinate the emetic reflex. The neurons coordinating the complex series of events that occur during emesis have been termed the "central pattern generator." Also, free radical formation appear to have an important role in the induction of nausea and vomiting.[12] The most important neurotransmitters which involve in emetic process are dopamine, serotonin and substance P. However, the receptors of 5-HT1A, 2A, 2C, 3A, 3B, 4, cannabioid 1 (CB1) and α-adrenergic are also known to be involved in emesis mechanism.[13] Moreover, μ-opioid receptors are also thought to be involved in mediating antiemetic effect in humans.[14]

The majority of dopamine, serotonin and substance P receptors are found in the dorsal vagal complex, the area postrema and in the gastrointestinal tract. After cytotoxic drugs have passed through the blood stream to the gastrointestinal tract, they can cause damage to the enterochromaffin cells. This damage causes subsequent release of 5-HT3 and stimulates the CTZ and vomiting center via 5-HT3 receptors. Ultimately, this causes contraction of abdominal muscles, diaphragm, stomach and esophagus activation and an emetic response.[10] The mechanism of CINV is depicted in Figure 2.1.

5-HT3 receptors are located centrally in the CTZ of the area postrema and peripherally in the vagal nerve terminals. Activation of the vomiting center is caused by direct stimulation of 5-HT3 receptors in the CTZ by cytotoxic drugs. Equally, stimulation of vagal afferents will be transmitted to the vomiting center through nucleus tractus solitarius.[15] Five different 5-HT3 receptors are known in humans, 5-HT3A, B, C, D and E. 5-HTR3A, 5-HTR3B and 5-HTR3C are expressed in the CNS as well as in the vagal nerve terminals, whereas 5-HTR3D is predominantly and 5-HTR3E is exclusively expressed in the gastrointestinal tract. The 5-HT3A and 5-HT3B receptor may be involved in the mechanism of CINV.[16]

Delayed and acute emesis mechanisms are thought to be different. Acute emesis is mainly stimulated by serotonin whereas dopamine and histamine are thought to contribute to delayed emesis. Some inflammation mediators, such as prostaglandine, histamine and substance P are involved in visceral inflammation which results in delayed emesis.[10] Otherwise, the Positron Emesis Tomography (PET), could be also useful to investigate the future pathophysiology of nausea and vomiting, especially in delayed emesis, refractory emesis and emesis during multiple cycles of chemotherapy.[17]

Pharmacology of antiemetic drugs

5-Hydroxytryptamine 3 receptor antagonists [5-HT3RAs]

The 5-HT3RAs are the standard antiemetic treatment for acute CINV in patients treated with moderately to highly emetogenic chemotherapy. It has been demonstrated that their use in combination with a corticosteroid results in complete protection of acute CINV in 70-80% of patients receiving highly emetogenic chemotherapy.[18,19] The 5-HT3RAs bind selectively and competitively to 5-HT3 receptors thereby blocking the emetogenic signals to the vomiting center.[15]

Several 5-HT3RAs, such as dolasetron, granisetron, ondansetron, tropisetron and palonosetron are available.[16] Table 2.3 shows the pharmacological characteristics of these 5-HT3RAs.

Generally, the 5-HT3RAs are well absorbed from the gastrointestinal tract and undergo first-pass metabolism after oral administration. The prodrug dolasetron is rapidly metabolized by carbonyl reductase to its active form, hydrodolasetron which is 70% bound to plasma proteins. This active metabolite is further metabolized mainly by cytochrome P450 [CYP] 2D6.[15]

Granisetron is metabolized by the liver through N-demethylation, aromatic ring oxidation, and conjugation mediated by the P450 CYP3A and CYP1A1 isoenzymes which is different from the other 5-HT3RAs. Ondansetron is 70-76% bound to plasma protein and is extensively metabolized by CYP3A4 in the liver by hydroxylation of the indole ring

Table 2.3 Pharmacokinetic characteristics of 5-HT3 receptor antagonists. Adapted from [13, 20, 49, 59].

	Ondansetron	Dolasetron	Granisetron	Tropisetron	Palonosetron
Oral bioavailability	60-70%	76%	60%	60%	97%
Volume of distribution	1.8 L/kg	5.8 L/kg	3.0 L/kg	5.7-8.6 L/kg	8.3 L/kg
Metabolism	CYP1A1* CYP1A2 CYP2D6 CYP3A4/5	CYP2D6 CYP3A4/5	CYP3A4/5 CYP1A1	CYP2D6 CYP3A4/5*	CYP2D6 CYP1A2* CYP3A4/5*
t1/2 elimination in healthy patients (hours)	3.5-5.5	6.9-7.3	4.9-7.6	5.7	24-64.2
t1/2 elimination in cancer patients (hours)	4	7.5	9-11	8	128

* Minor.

followed by glucuronide or sulfate conjugation.Tropisetron is metabolized mainly by the liver P450 CYP2D6 isoenzyme through oxidative hydroxylation of the indole ring followed by conjugation with glucuronic acid or sulfate which are excreted by the kidneys.[15,20]

Palonosetron is 62% bound to plasma proteins. Palonosetron's total clearance is lower than the other 5-HT3RAs resulting in a relatively long plasma elimination half-life.[21] Palonosetron is metabolized mainly by CYP2D6 (50%) and followed by CYP3A and CYP1A2 mediated metabolism.[15]

Granisetron, ondansetron and palonosetron have slightly different receptor specificity. Palonosetron is a highly selective, high affinity competitive antagonist of the 5-HT3A receptor, whereas granisetron is highly specific for all subtypes of 5-HT3 receptors but has little or no affinity for 5-HT1, 5-HT2 and 5-HT4 receptors. Ondansetron also binds to the 5-HT1B, 5-HT1C, α1-adrenergic and μ-opioid receptors. The clinical relevance of these findings is not clear.[15] Despite the fact that ondansetron has different affinity to 5-HT3B,1B,1C, α-adrenergic and μ- opioid receptors as compared to granisetron, many studies have shown that this not imply differential efficacy between ondansetron and granisetron.[13]

Dopamine antagonists

The exact mechanism of action of the dopamine antagonists, prochlorperazine and metoclopramide as antiemetic drugs is unclear, but prochlorperazine inhibits apomorphine-induced vomiting by blocking dopamine D2 receptors [DRD2] in the CTZ. Also metoclopramide has shown to directly affect the CTZ in the area postrema by blocking DRD2. The drug increases the CTZ threshold and decreases the sensitivity of visceral

nerves that transmit afferent impulses from the gastrointestinal tract to the vomiting center in the lateral reticular formation.[22]

The phenothiazine derivative prochlorperazine is primarily metabolized in the liver via hydroxylation, oxidation, demethylation, sulfoxide formation and conjugation with glucuronic acid. The oxidative reactions are catabolized by CYP2D6. Metoclopramide is also metabolized by the liver and its metabolites are excreted in the urine and feces.[22,23] CYP2D6 plays a major role in metoclopramide metabolism, thus poor metabolizer of CYP2D6 may have slower elimination of metoclopramide.[24] Also the buthyrophenone haloperidol shows extensive hepatic metabolism with CYP3A4 being the main enzyme involved.[25,26]

Corticosteroids

Corticosteroids such as dexamethasone are potent antiemetics and are used in combination with other agents. Their antiemetic mechanism of action is uncertain but it is assumed that it involves inhibition of the prostaglandin synthesis in the hypothalamus.[26]

Corticosteroids are metabolized in most tissues, but primarily in the liver through glucuronidation and sulfoxidation pathways to biologically inactive compounds.[22] Dexamethasone and methylprednisolon are substrates of CYP3A4.[13]

Benzodiazepines

The antiemetic mechanism of action of benzodiazepines, for example lorazepam, is related to the combination effects of sedation, reduction in anxiety, and possibly depression of the vomiting centre.[22,26]

Benzodiazepines bind to plasma protein, varying from 70-99%, and undergo extensive metabolism by CYP enzymes.[27] The CYP2C19 and CYP3A4/5, CYP2C9 and CYP1A2 contribute to the metabolism of benzodiazepines.

Cannabinoids

Cannabinoids have an antiemetic effect at the enterochromaffin cells in the gastrointestinal tract and an anti-cholinergic effect on cholinergic terminals and Auerbach's plexus and possibly mediate the prostaglandin cyclic nucleotide system.[26] Two cannabinoid drugs, dronabinol and nabilone, have been approved for CINV. Although there are conflicting data, cannabinoids can be used for refractory emesis.[23,28,29] Nabilone showed superior efficacy compared to prochlorperazine and also the combination of the two agents were better than was used alone.[30] The use of these agents is limited because of their slow elimination from the

body and because of adverse effects such as sedation, dysphoria, vertigo, euphoria, dizziness, and dry mouth.[29] Cannabinoids are prone to pharmacodynamic and/or pharmacokinetic interactions with other drugs. The interaction of cannabinoids with chemotherapeutic agents that are sensitive to the alteration of CYP3A function should be closely monitored.[31]

Antihistamines

The pharmacological effect of the antiemetic drug dimenhydrinate is conceived as result of its diphenhydramine moiety. Dimenhydrinate and meclizine have CNS depressant, anti-cholinergic, antiemetic, antihistamines and local anesthetic effects. Although its antiemetic mechanism of action is unclear, dimenhydrinate has been shown to inhibit vestibular stimulation, acting first on the otolith system and in larger doses on the semicircular canals. Dimenhydrinate inhibits acetylcholine and it is proposed that this is the primary mechanism of action. Dimenhydrinate is widely distributed into body tissues, and is metabolized by the liver via CYP450, but limited information is available on which specific isoenzyme is involved.[22]

Neurokinin-1 antagonist

Aprepitant is a neurokinin-1 receptor antagonist and inhibits the action of substance P in the emetic pathways both centrally and peripherally. Substance P, neurokinin-A (NK-A) and neurokinin-B (NK-B) are members of the tachykinin family. These peptides are mediated through three receptors: NK-1, NK-2, NK-3. Substance P displays the strongest affinity for NK-1, whereas NK-A and NK-B have strong affinity for NK-2 and NK-3.[32] Recently, substance P has shown to have a role in emesis, especially in delayed emesis.[33]

Aprepitant is highly bound to plasma proteins (> 95%) and has an elimination half life of 9-13 hours making it suitable for once daily administration. Aprepitant is both a substrate and a moderate inhibitor of CYP3A4. In addition, aprepitant also induces CYP2C9 and CYP3A4 and therefore may be prone to drug-drug interactions.[32]

Casopitant, a new yet unapproved neurokinin-1 receptor antagonist, has an oral clearance of 24.4 L/h/kg in female patients and this agent is both a substrate and weak to moderately inhibitor of CYP3A4.[34]

Variable efficacy of antiemetics

According to the guideline of the American Society of Clinical Oncology on prevention of CINV, the combination of neurokinin-1 receptor antagonist, 5-HT3RA and dexamethasone is the regimen of choice in patients receiving highly emetogenic chemotherapy. Moreover,

addition of lorazepam or alprazolam, or substitution the 5-HT3RA with high dose intravenous of metoclopramide or adding dopamine antagonist is recommended in patients with suboptimal response.[7,8]

5-Hydroxytryptamine 3 receptor antagonists [5-HT3RAs]

The use of 5-HT3RAs and the combination with dexamethasone results in complete acute emesis protection in 70% of patients receiving a first cycle of highly emetogenic chemotherapy. However, they are not very effective in the delayed phase of emesis. Indeed, even following complete protection in the acute phase, 40% of patients experience delayed symptoms of emesis, which interfere with quality of life. In the outpatients setting, the symptoms may be underestimated by health care professionals.[2]

Tropisetron, ondansetron and granisetron are considered to have similar efficacy which is supported by several clinical studies. A Turkish study showed that the complete response rate of these drugs in combination with dexamethasone in the control of acute emesis was 80% for tropisetron 72% for ondansetron and 72% for granisetron ($P = 0.877$). These three drugs also appeared to have similar side-effect profiles.[35]

Palonosetron was found to be effective in preventing delayed CINV and it was approved by FDA as the first antiemetic drug for preventing both acute and delayed CINV.[10] It has a higher binding affinity and longer elimination half life as compared to the other 5-HT3RAs due to its unique structural characteristics based on a fused tricyclic ring system.[36,37] The use of palonosetron, aprepitant and dexamethasone as a single day regimen of antiemetic combination in cancer patients receiving cyclophosphamide and/or doxorubicin resulted in complete protection in 51% of patients with 76% of patients in acute phase and 66% of patients in delayed phase of emesis.[38] The use of this combination in Japanese patients showed protection in 75% of patients in the acute phase compared with 73% in the granisetron group. During the delayed phase 57% of patients had complete response in the palonosetron group compared to 45% of patients in granisetron group.[39]

Ramosetron and azasetron are the newest agents of 5-HT3RA. In cancer patients receiving highly and moderately emetogenic chemotherapy, the combination of intravenous ramosetron and dexamethasone showed 77% of complete response in comparison with granisetron and dexamethasone which had 82% of complete response.[40]

Azasetron, in combination with olanzapine and dexamethasone could improve the complete antiemetic response of cancer patients in the delayed phase. In this study the combination of azasetron-dexamethasone and olanzapine-azasetron-dexamethasone was compared in patients receiving highly and moderately emetogenic chemotherapy.[41]

Dopamine antagonists

Metoclopramide is still used for breakthrough CINV symptoms and as adjunctive medications in building antiemetic regimens for patients with refractory nausea and vomiting. Prochlorperazine has similar efficacy as ondansetron plus dexamethasone in preventing delayed nausea vomiting on days 2 to 5.[42] However, the use of metaclopramide in pediatric and elderly patients is not recommended because of the high incidence of dystonic reactions.[8,43]

Corticosteroids

The complete response rates of dexamethasone are about 15-20% higher when it was added to 5-HT3RAs. Dexamethasone is effective in prevention of CINV in both the acute phase and delayed phase. Corticosteroids are sometimes underutilized because of their potential adverse effects. Because the antiemetic use of corticosteroids is short term, tapering the dose is rarely needed.[29]

Benzodiazepines

Benzodiazepines, especially lorazepam are being used for patients with breakthrough symptoms and anticipatory symptoms of CINV.[8,23] Olanzapine can improve both patients' quality of life and patients' complete response in delayed nausea vomiting during the treatment of highly or moderate emetogenic cytostatics.[41] In a phase II study, the combination of olanzapine, dexamethasone and palonosetron was effective in controlling acute nausea and vomiting in patients receiving highly and moderately emetogenic cytostatics.[44]

Cannabinoids

Nabilone as antiemetic was superior to placebo, domperidone and prochlorperazine in preventing CINV, but not superior to metoclopramide or chlorpromazine. Nabilone also did not increase the benefit of 5-HTRAs as antiemetic in CINV.[45] The use of cannabinoids and olanzapine have been suggested as potentially useful interventions, but data from phase III clinical trials are still lacking.[46]

Antihistamines

Diphenhydramine or hydroxyzine in the prevention of CINV have not shown any antiemetic activity. Antihistamines have a role in the treatment of nausea thought to be mediated by the vestibular system.[3]

NK-1 antagonist

There is evidence to support the use of a three-drug regimen for prevention of acute emesis in highly emetic regimens as a minimum standard of care, including a 5-HT3RA, a neurokinin-1 antagonist and dexamethasone.[10,11] A randomised phase II study of the NK-1 antagonist aprepitant in patients receiving cisplatin showed a complete protection in the NK-1 antagonist arm of the study of 93% for acute emesis and 83% for delayed emesis compared to 67% for acute emesis and 37% of delayed emesis with granisetron and dexamethasone. The addition of aprepitant to the 5-HT3RA and dexamethasone can improve the acute emesis protection by a further 10-15% and 20-30% in the delayed phase of emesis.[19]

The efficacy of casopitant was shown in study comparing the combination of casopitant-ondansetron-dexamethasone and ondansetron-dexamethasone. The addition of casopitant could increase the complete antiemetic response at 120 hours by 20% in cancer patients receiving highly emetogenic chemotherapy.[47]

Aprepitant is not available in some countries, and the 5-HT3RAs are relatively expensive and may therefore not be an option for some patients. Other agents such as prochlorperazine, nabilone, dronabinol and olanzapine may be added, however no studies are available on the efficacy and safety of these combinations.[46]

General remark concerning variable clinical efficacy of antiemetic drugs

The effectivity of antiemetic treatment is also influenced by factors such as age of the patients, history of alcohol intake, type of cancer, chemotherapy regimen and course of chemotherapy. There are data available from gynaecologic cancer patients showing that younger patients who received cisplatin regimen experience significant lower rates of nausea and vomiting complete responses. However, patients with the first three course of chemotherapy had significant higher complete response with regard to nausea than those with chemotherapy after the third course.[48] The 5-HT3RAs with long duration of action, low risk of drug-drug interactions and once daily dosing are preferred.[49] Combination of palonosetron and dexamethasone shows no significant differences in complete response and complete control of emesis in elderly patients (≥ 65 years) as compared to non-elderly patients (< 65 years) who received high and moderate emetogenic cytostatic agent (P = 1.00).[50] In cancer patients with multiple-day chemotherapy, the efficacy of the combination of palonosetron and dexamethasone is not significantly different compared to ondansetron and dexamethasone in prevention of delayed emesis. Nevertheless, patients still need rescue antiemetic treatment to a considerable extent.[37] Female gender and a history of motion sickness is positively related to efficacy to prevent nausea in patients receiving

combination of 5-HT3RA and dexamethasone. In addition, patients with a history of low chronic alcohol intake experienced more post chemotherapy vomiting.[51]

Pharmacogenetic studies of antiemetics

Differential responses of patients to antiemetic drugs can be due to factors such as age, gender, and variations in the activity of enzymes, which are involved in the uptake, binding, activation or degradation of these drugs. Table 2.1 summarizes the published pharmacogenetic studies of antiemetics. The pharmacogenetic studies about DRD2 antagonists related with their usage as antiemetics are not found. No pharmacogenetic studies on corticosteroids used as antiemetic are known.

Pharmacogenetic studies exploring variation in genes encoding drug receptors

Tremblay et al.[52] performed a pharmacogenetic study in German Caucasian cancer patients (n = 242), who received moderately to highly emetogenic cytostatic drug regimens. Prophylactic tropisetron or ondansetron during chemotherapy was given to the patients. In total, 13 polymorphisms in the *5-HT3B* receptor gene were studied and the frequencies of these variants ranged from 0.4% to 0.7%. Homozygotes for the -100_-102AAG deletion variant in the promoter region of *5-HT3B* receptor gene experienced significantly more vomiting and nausea. Patients homozygous for the -100_-102AAG deletion variant of the *5-HT3B* receptor gene showed the highest intensity of vomiting and nausea after chemotherapy, whereas the patients having the wild type showed the lowest score [mean value of episodes of vomiting in the first observation period of 1 ± 0.58 v 0.23 ± 0.07; P = 0.02]. The intensity of vomiting of heterozygous carriers of the deletion variant was in between the intensity of vomiting observed in the homozygous mutant and the wild type carriers. The Odds Ratio (OR) for nausea and vomiting was 0.5 [95% CI: 0.1-3.2] in the heterozygous carriers of the deletion variant and 32 in homozygous carriers of the deletion variant [95% CI: 2.5-422] after adjustment for the other predictors of nausea and vomiting, such as age, female gender, glucocorticoids usage, and the variant of *CYP2D6*. However, the frequency of the heterozygous genotype for the deletion variant is approximately 20% whereas the frequency of the homozygous genotype is only 1.3%. Moreover, the data warrant confirmation with larger sample sizes.

Kaiser et al.[6] investigated polymorphisms of the 5-HT3A receptor in 242 Caucasian cancer patients with various emetogenic treatments. They included 21 polymorphisms with an allele frequency of the variant ranging from 0.2% to 31.1% in their study. The number of patients suffering from nausea was 35.9% and higher than the number of patients with emesis (23.7%). No significant association between efficacy and genetic variants

was found. Only patients with the heterozygous Met257Ile polymorphism showed a non-significantly lower intensity of nausea and vomiting compared to wild type patients. However, the frequency of the Met257Ile variant is very low and there was no single individual homozygous for the Met allele. The 5819G>A polymorphism showed a non-significant higher intensity of nausea and vomiting compared to patients homozygous for the G allele. The authors suggest to consider a combination of individual risk factors such as age, gender, the emetogenicity level of cytotoxic drug and the polymorphism of *CYP2D6*, as a predictor of emesis risk while a single genetic polymorphism in the *5-HT3A* receptor gene may not serve as a pharmacogenetic predictor of antiemetic treatment with 5-HT3RAs in cancer patients.[6]

A study on polymorphisms of the *5-HT3C* receptor gene in 70 Caucasian cancer patients receiving dolasetron or ondansetron was performed by Ward et al. The study revealed seven novel variants in the *5-HT3C* gene with allele frequencies ranging from 1.4% to 42.9%. The common polymorphisms were 6342C>T, 7051G>A and 7142G>C. There were no statistically significant associations between either isolated variants or haplotypes and antiemetic efficacy. About 18.6% of patients failed to achieve the optimal protection and 28.6% of patients experienced nausea. This study concluded that genetic variants of the 5-HT3C receptor genes may not predictive for antiemetic response of the used drugs.[53]

Fasching et al.[54] studied 120 Caucasian cancer patients receiving a combination of ondansetron-dexamethasone before anthracycline chemotherapy. They explored 1 SNP in *5-HT3B* receptor gene (Y129S) and 2 SNPs in *5-HT3C* receptor gene (A405G and K163N) with an allele frequency ranging from 29.9% to 62.1%. The Y129S and A405G showed no significant association with the complete response of emesis. However the K163N variant was found to be significantly associated with a higher percentage of non responders. Wild type and heterozygous patients were reported to have a vomiting episode rate of 22%, whereas homozygous patients were reported to have a vomiting episode in 50% of the patients. The homozygous variants of K163N had hazard ratio of 3.35 (95% CI, 1.00-11.25) in comparison with the heterozygous patients in acute emesis. Therefore, the *HTR3C* gene could serve as a predictive factor for CINV in patients undergoing moderately emetogenic chemotherapy.

Pharmacogenetic studies exploring variation in genes encoding enzymes involved in drug metabolism

The highly polymorphic cytochrome P450 mono-oxygenase system in the liver is involved in the metabolism of many drugs. About 20 to 25% of all drugs in clinical use are metabolized at least in part by CYP2D6.[55] CYP2D6 activity may be classified into

one of four categories: 1) poor metabolizers (PM), 2) intermediate metabolizers (IM), 3) extensive metabolizers (EM), 4) ultrarapid metabolizers (UM).[52] The majority of the Caucasian population is classified into EM, 5-10% are PM, approximately 2% are UM whereas less than 2% of Asians were found to be PM and more than 50% were found to be EM.[15,53] The frequency of dysfunctional CYP2D6 alleles in Asians is 50% and higher than in Caucasians (29%). Therefore, many Asians, including Japanese, Chinese and Malay, metabolize CYP2D6 mediated drugs more slowly than Caucasians, because of predominantly CYP2D6*10, a highly frequent reduced function allele. Kaiser et al studied the clinical impact of genetic polymorphisms in the *CYP2D6* gene on 5-HT3RAs response in cancer patients. Caucasian patients who were UMs had more vomiting within the first 4-h ($P = 0.001$) and within the 5 to 24 h period ($P = 0.03$) when given ondansetron and tropisetron as prophylactic therapy. This result was supported by the observation that tropisetron is primarily dependent on the CYP2D6 isoenzyme for metabolism. The frequency of UMs in Caucasians is low (1.5%) and the study must be confirmed with larger sample sizes to define the contribution of genotyping.[20]

In a study investigating patients' response to ondansetron prophylaxis for post-operative nausea and vomiting ($n = 250$), there were significant differences of vomiting incidence in PM, IM, EM and UM (8%, 17%. 15% and 45%, $P < 0.01$) but not in nausea incidence.[56]

Variation in genes encoding drug transporters

A study in cancer patients ($n = 216$) receiving high or moderate emetogenic cytostatic drugs which were given prophylactic tropisetron, ondansetron or granisetron was performed to explore an association of *ABCB1 3435C>T* polymorphism with clinical resistance to 5-HT3RAs. Overall the proportion of patients who were protected from nausea and vomiting was about 60% in the acute phase and 50% in the delayed phase of chemotherapy. Patients who were homozygous for the *ABCB1 3435T* allele responded better to antiemetic therapy (92.9%) compared with individuals who were heterozygous (56.1%) or homozygous for the *ABCB1 3435C* allele (47.6%) in the acute phase ($P = 0.044$). This difference reached statistical significance in the granisetron-treated group. However, no statistically significant differences were found in the patients treated with tropisetron or ondansetron, which is surprising since ondansetron is known to be transported by ABCB1 whereas tropisetron is not. It is likely that patients with the TT genotype accumulate higher concentrations of 5-HT3RAs in the brain and may benefit more from 5-HT3RA treatment. During the delayed phase of chemotherapy, there were no differences in the proportion of complete control of emesis across the genotype groups ($P = 0.53$). The findings of this study need to be confirmed in a cohort treated with a more homogeneous chemotherapeutic regimen and at a larger sample size.[57]

Conclusion

Despite a wide armamentarium of antiemetic drugs a considerable number of cancer patients treated with emetogenic chemotherapy experience nausea and vomiting. Pharmacogenetics may help to individualize antiemetic treatment however this field is relatively unexplored. Interestingly, drug transporters, metabolism and receptor target pathways of 5HT3RAs are known to be polymorphic and have shown to be related to efficacy of 5-HT3RAs. However, it is too early to implement the results of the various studies into clinical practice. Additional large studies also considering non-genetic risk factors are warranted.

Impact of findings on practice

- Since only limited pharmacogenetic studies of antiemetic in oncology are known, the clinician's decision regarding antiemetic treatment are currently based on patient's risk factors and profile of emetogenicity of chemotherapeutic drugs rather than on genetic variants affecting antiemetic drug reponse.
- Genetic variant should be only considered in case of suboptimal antiemetic response in patients treated with highly emetogenic chemotherapy.
- Other investigators may be encouraged to conduct the pharmacogenetic studies on antiemetic drug treatment in oncology.

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3

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*

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ABSTRACT

Objective: Suboptimal treatment of chemotherapy-induced nausea and vomiting (CINV) 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 ≥ 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, 3 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 acute and delayed phase. The following single nucleotide polymorphisms were determined in *ABCB1*: rs1045642, rs2032582, rs1128503; in *5-HT3B receptor*: rs45460698, rs4938058, rs7943062 and in *CYP2D6*: rs16947 (*CYP2D6*2*), rs3892097 (*CYP2D6*4*), 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 CTG haplotype of the *ABCB1* gene experienced Grade 3 and 4 CINV 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 CINV.

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 hours after chemotherapy, may be used as predictor of delayed CINV.[3] However, patients with delayed CINV, which persists from 24 to 120 hours after chemotherapy, experience more severe impact of daily functioning than patient 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 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 hours until 120 hours 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 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, 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 a 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 (UM) 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 protein transporter and 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 of 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 ≥ 50 mg/m^2 as monotherapy or in combination chemotherapy regimens. Ondansetron 8 mg intravenously and dexamethasone 8 mg intravenously were standard antiemetic therapy for prevention of acute CINV. Metoclopramide, 10 mg orally, 3 times per day as fixed presciption, 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 ≥ 18 years old with a Karnofsky performance scale (KPS) of ≥ 50%. We used self-reported ethnicity. However, to make a more accurate assessment of ethnicity also the ethnicity of the parents and grandparents were verified. Exclusion criteria were: the presence of nausea or vomiting 24 hours before chemotherapy; the use of other antiemetics such as benzodiazepines or neuroleptics, radiotherapy within

24 hours before 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 x ULN for patients without liver metastases > 5 x 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 minute from the previous one counted as 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 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 less than a 5 score on the NVAS scale, while patients with delayed emesis (yes) were patients with vomiting and/or scored ≥ 5 scale of NVAS.[24,25]

SNPs selection and genotyping assays

Three 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), rs1128503 (exon 12) and three SNPs of *CYP2D6*; rs16947 (CYP2D6*2), rs3892097 (CYP2D6*4), 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 analysed on ABI 7500 realtime PCR System from Applied Biosystems (Nieuwerkerk aan den IJssel, The Netherlands) according to manufactures' protocol of allelic discrimination. As a quality control at least 5% of samples were genotyped in duplicate and no inconsistencies were found. Overall genotyping success rate of the samples was more than 96%.

Statistical methods

The genotype frequencies were assessed for deviations from Hardy Weinberg equilibrium and they did not deviate from 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 phases consideration was ≥ 0.01.[30]

The predicted phenotypes of SNPs in 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 definition of extensive metabolizers (EMs) include *2/*2, *2/*10, the intermediate metabolizers (IMs) include *2/*4, *4/*10, *10/*10, and poor metabolizers (PMs) include *4/*4.

The χ^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 χ^2 test. These associations are considered to be the result of ondansentron as the antiemetic drug in the acute phase and metoclopramide as the antiemetic drug in delayed phase. A *P* value of < 0.05 was considered as 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 3.1 presents the patient characteristics.

Table 3.1 Characteristics of cancer patients treated with antiemetics (n = 202)

Characteristic		
Age (mean ± SD)	48.6 ± 9.6	
Gender	*n*	%
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
Stage of cancer		
Stage I and II	139	68.8
Stage III and IV	63	31.2
Cytostatic agent		
Cisplatin	81	40.1
Cisplatin and other agent	121	59.9
Cisplatin dose		
50-70 mg/m^2	183	90.6
75-100 mg/m^2	19	9.4
BMI		
Underweight (16-18.5 kg/m^2)	49	24.3
Normal (18.5-25kg/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
Comorbidity		
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
NA	23	11.4
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

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, 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 3.2.

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. Figure 3.1 and Figure 3.2 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 3.3 depicts the association between patient characteristics and primary and secondary outcome measurements. No significant associations of patient characteristics and primary 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 3.4 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

Table 3.2 The occurrence of acute and delayed chemotherapy induced nausea and vomiting

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

CINV, chemotherapy induced nausea vomiting.

the delayed phase. Carriers of the *ABCB1* CTG haplotype experienced more frequent Grade 3/4 CINV compared to 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.

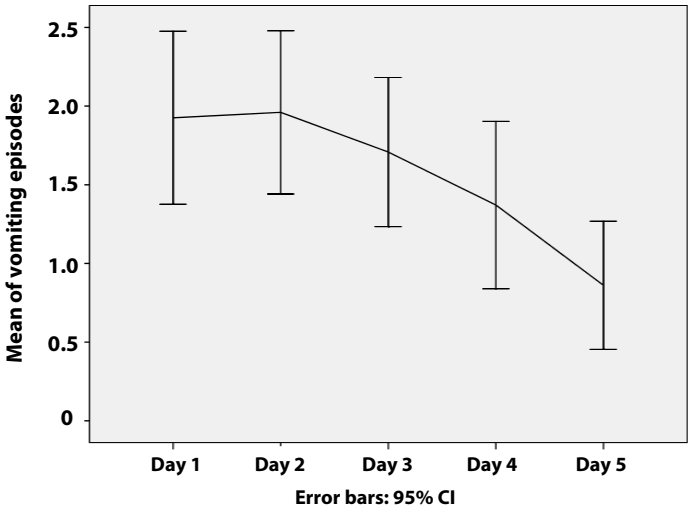

Figure 3.1 Mean (± SD) number of vomiting episodes over 5 days after initiation of chemotherapy.

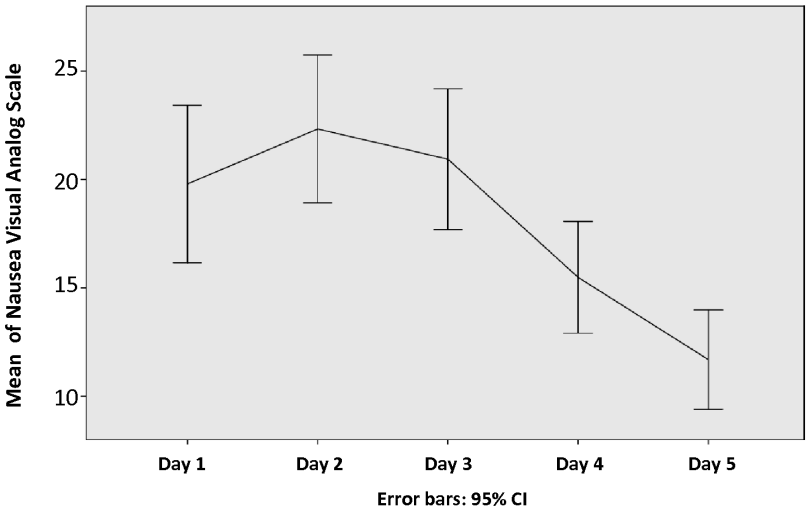

Figure 3.2 Mean (± SD) of Nausea Visual Analog Scale over 5 days after initiation of chemotherapy.

Table 3.3 Univariate analysis of patients characteristics and primary-secondary outcome

Patients characteristics	Acute nausea [*n* (%)		*P* value	Acute vomiting [*n* (%)]		*P* value	Delayed CINV		*P* value
	Grade 1 & 2 (*n* = 158)	Grade 3 & 4 (*n* = 44)		Grade 1 & 2 (*n* = 141)	Grade 3 & 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)		79 (63.7)	42 (53.8)	0.31
Ovarian cancer	46 (29.1)	12 (27.3)		39 (27.7)	19 (31.1)	0.46	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									
Stage 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
Stage 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)	
Comorbidity									
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	97 (61.4)	26 (59.1)	0.78	91 (64.5)	32 (52.5)	0.11	74 (59.7)	49 (62.8)	0.66
No	61 (38.6)	18 (40.9)		50 (35.5)	29 (47.5)		50 (40.3)	29 (37.2)	
Yes									
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 3.4 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
	Grade 1 & 2	Grade 3 & 4		Grade 1 & 2	Grade 3 & 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)		82 (60.3)	28 (53.8)		67 (56.3)	43 (62.3)	
Carrier of CCG haplotype	63 (42.0)	15 (39.5)	0.78	54 (39.7)	24 (46.2)	0.42	52 (43.7)	26 (37.3)	0.42
CTG									
Other haplotypes	76 (50.7)	22 (57.9)		68 (50.0)	30 (57.7)		70 (58.8)	28 (40.6)	
Carrier of CTG haplotype	74 (49.3)	16 (42.1)	0.43	68 (50.0)	22 (42.3)	0.35	49 (41.2)	41 (59.4)	0.02*
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									0.90
Other haplotypes	60 (40.0)	12 (31.6)		53 (39.0)	19 (36.5)		46 (38.7)	26 (37.7)	
Carrier of TTT haplotype	90 (60.0)	26 (68.4)	0.34	83 (61.0)	33 (63.5)	0.76	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)		32 (24.4)	12 (21.8)				
Carrier of AAGAG haplotype	116 (77.3)	26 (72.2)	0.52	99 (75.6)	43 (78.2)	0.70			
AAGGG									
Other haplotypes	106 (70.7)	21 (58.3)		87 (66.4)	40 (72.7)				
Carrier of AAGGG haplotype	44 (29.3)	15 (41.7)	0.15	44 (33.6)	15 (27.3)	0.40			
AAGAA									
Other haplotypes	112 (74.7)	30 (83.3)		99 (75.6)	43 (78.2)				
Carrier of AAGAA haplotype	38 (25.3)	6 (16.7)	0.28	32 (24.4)	12 (21.8)	0.70			
Del AG									
Other haplotypes	107 (71.3)	26 (72.2)		96 (73.3)	37 (67.3)				
Carrier of delAG haplotype	43 (28.7)	10 (27.8)	0.92	35 (26.7)	18 (32.7)	0.41			
CYP2D6 predicted phenotype	*n* = 150	*n* = 37		*n* =133	*n* = 54		*n* = 117	*n* = 70	
EM	93 (62.0)	28 (75.7)		86 (64.7)	35 (64.8)		76 (65.0)	45 (64.3)	
IM	57 (38.0)	9 (24.3)	0.12	47 (35.3)	19 (35.2)	0.98	41 (35.0)	25 (35.7)	0.93

* significant value. EM, extensive metabolizers; IM, intermediate metabolizers; CINV, chemotherapy induced nausea vomiting.

DISCUSSION

Our study confirms that prevention of CINV is suboptimal, ondansetron and dexamethasone could prevent about 80% of patients from acute nausea and 70% of 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, patients-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 CTG haplotype in *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 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 *5-HT3B* receptor gene, although it did not reach statistical significance. Patients carrying the deletion AG haplotype in 5-HT3B receptor experienced a lower grade of nausea and a higher grade of vomiting in the acute phase compared to 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 *ABCB1* gene and the -100_-102 AAG deletion variant of *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 *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 the 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 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 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 CTG haplotype of *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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4

Differences in 5-Hydroxytryptamine-3B haplotype frequencies between Asians and Caucasians

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ABSTRACT

Background: The 5-hydroxytryptamine 3 (5-HT3) receptor is a ligand-operated ion channel with five different receptor subunits (5-HT3A, B, C, D, and E) found in humans. Activation of 5-HT3 receptors causes various effects such as drug-induced emesis and behavioral effects such as anxiety, depression and cognitive disorders. To explore interethnic differences in 5-HT3 receptor antagonists response, we studied haplotype frequencies in the gene encoding the 5-HT3B receptor in Asians and Caucasians.

Methods: Three SNPs of *5-HT3B* receptor gene, deletion AAG in 5'-UTR position, 18792A>G in intron position and 46698G>A in 3' near gene position were selected and genotyped in 165 Indonesian cancer patients and 188 Caucasian healthy volunteers. Haplotypes were set with gPlink, whereas the difference in haplotype frequencies between Indonesians and Caucasians was compared using multivariate analysis.

Results: The haplotype profiles based on the deletion AAG, 18792A>G and 46698G>A were AAGAA, AAGAG, AAGGG and deletion AG in both of Indonesians and Caucasians. The frequency of the AAGAG haplotype in Indonesians was 54.8% and in Caucasians it was 39.9% ($P < 0.05$). The frequency of AAGGG haplotype in Indonesian was 14.3% and in Caucasians was 29.3%. Moreover, there were significant differences the frequencies of haplotype pairs between Indonesian and Caucasian ($P < 0.001$).

Conclusion: Indonesian cancer patients had significantly different AAGAG and AAGGG haplotype frequencies of the gene encoding the 5-HT3B receptor compared to healthy Caucasians. This finding could be useful for understanding interethnic differences in drug response of drugs targeting the 5-HT3B receptor in cancer treatment related emesis.

INTRODUCTION

The 5-hydroxytryptamine-3 (5-HT3) receptor is a ligand-operated ion channel.[1] This receptor is found in abundance on parasympathetic terminals in the gastrointestinal tract, on the nucleus tractus solitarii and area postrema of central nervous system (CNS).[2] Therefore, this receptors contribute to neuropsychiatric function and the regulation of gastrointestinal functions.[3]

Until now, there are five different receptor subunits of the 5-HT3 receptor in humans: 5-HT3A, B, C, D, and E. The 5-HT3A, B and C are most expressed in the CNS and in the peripheral nervous system, whereas the 5-HT3E receptor is mainly and the 5-HT3D predominantly expressed in the gastrointestinal tract, with the activation of 5-HT3 receptors resulting in various effects, such as emesis and behavioral effects, such as anxiety, depression and cognitive disorders.[4]

Several studies in Caucasians have shown an association between polymorphisms in the gene encoding the 5-HT3B receptor and antiemetic response to 5-HT3 receptor antagonists. 5-HT3 receptor antagonists are frequently used in the prevention and treatment of emesis and vomiting related to drug treatment.[5,6] In addition, some variants of the gene encoding this receptor subtypes have been thought to contribute to neurological and psychiatric disorders.[5] Specifically, the pharmacogenetic studies of genetic variants of the 5-HT3B receptor showed that the deletion AAG at position 100 to 102 was significantly associated with failure of response to 5-HT3B receptor antagonists in chemotherapy-induced nausea and vomiting in Caucasians.[6] In Japanese patients with depressive and anxiety disorders, this variant was associated with paroxetine-induced emesis, next to major depression and etiology of bipolar affective disorders.[6,7] Finally, another study explored possible associations between genetic polymorphisms in nine exons of gene encoding the 5-HTR3B receptor in relation to the occurrence of postoperative nausea and vomiting. This study suggests that 5-HT3B receptor variants may have significant impact on the incidence of postoperative nausea and vomiting.[8]

Today, only limited data are available on haplotypes in the gene encoding the 5-HT3B receptor in Asian population. The aim of this study was therefore to establish allele and haplotype frequencies of the 3 single nucleotide polymorphisms (SNPs) in the gene encoding 5-HTR3B receptor; rs45460698 (deletion AAG in 5'-UTR position), rs4938058 (18792A>G in intron position), and rs7943062 (46698G>A, in 3' near gene position) in Asians and to compare the frequencies with those of a Caucasian population.

METHODS

Population

DNA from 165 Indonesian cancer patients and from 188 Caucasian healthy volunteers was collected for genetic analysis. The Caucasian subjects were men (66%), women (34%) with a mean of age 46.4 ± 13.3 (mean ± SD). However these numbers were calculated from 96 subjects of 188 Caucasian subjects, because the blood donation foundation (Sanquin, The Netherlands) did not provide the characteristics of the remaining donors. The Indonesian cancer patients were recruited at the Sardjito hospital Yogyakarta between January 2009 and November 2009. Most of the cancer patients were women (89.1%) with the diagnoses of cervical cancer (58.8%), ovarian cancer (24.8%), vulva cancer (0.6%) and other cancer (15.8%); the remaining patients were men (10.9%) with a diagnoses of nasopharyngeal cancer. They were first diagnosed as cancer patients at stage I and II (69.1%) and stage III and IV (30.9%). These patients were treated with cisplatin, considered as highly emetogenic chemotherapy and received antiemetics as well. DNA from these subjects was isolated from saliva samples using Oragene™ DNA self-collection kit (DNA Genotek Inc., Ottawa, Ontario, Canada) according to manufacture's prescription. DNA derived from anonymized Caucasian healthy volunteers, was isolated from EDTA anti-coagulated blood using the MagnaPure Compact (Roche Diagnostics, Almere, The Netherlands). The Institutional Review Board of Gadjah Mada University, Yogyakarta, Indonesia approved the study and gave informed consent before enrolment in the study. DNA was quantified using Nanodrop (Isogen, Maarssen, The Netherlands).

Genotypes were established using Taqman assays and analysed on ABI 7500 realtime PCR System from Applied Biosystems (Nieuwerkerk aan den IJssel, The Netherlands) according to the manufacturer's protocol.

Polymorphism selection

Three SNPs in the *5-HT3B* receptor gene, rs45460698 (deletion AAG in 5'-UTR position), rs4938058 (18792A>G in intron position), and rs7943062 (46698G>A, in 3' near gene position) were selected from the National Center for Biotechnology Information (NCBI) SNP database. There were 4 criteria for selection of the SNPs: 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 in *5-HTR3B* receptor gene (D-prime value = 1 and $r^2 \geq 0.7$) and/or indications for relevance based on previous publications.

The SNP rs45460698 was chosen based on the associations with antiemetic response to 5-HT3RAs as shown in previous studies.[8,9] The SNP rs45460698 was chosen based on the associations with antiemetic response to 5-HT3 receptor antagonists as shown in previous studies [8,9]. The SNP rs4938058 is in LD with 6 other SNPs (rs7103572, rs11214769, rs12270070, rs2276307, rs4936285, rs12795805) and the rs7943062 is in LD with the rs11214763 SNP and they were therefore chosen as tagging SNPs. In contrast to the rs45460698 SNP, the rs4938058 and rs7943062 SNPs were not specifically studied in relation to 5-HT3 receptor antagonist response but it is expected that any functional variant in the gene encoding the 5-HT3 receptor will potentially influence the response to the HT3 receptor antagonists and therefore these 2 SNPs were also included in the study.

A challenge in any candidate gene pharmacogenetic study is the selection of polymorphisms. We applied several selection criteria under the assumption that these criteria increased the informative value of the SNP in relation to clinical and functional effects on the gene. However, the *HTR3B* gene is highly polymorphic meaning that our SNPs only represent only a fraction of the possible variation in the population.

5-HT3B receptor gene haplotypes

For the estimation of haplotype frequency and the setting of individual haplotypes from raw genotype data we used the gPlink software with default settings. The estimation of haplotype frequencies/phases was above or equal to 0.01 and phases consideration was above or equal to 0.01 (http://pngu.mgh.harvard.edu/~purcell/plink/index.shtml, accessed on 22 August 2010).

Statistical analysis

The genotype frequencies were assessed for deviations from Hardy Weinberg equilibrium. The differences in haplotype frequency between Indonesians and Caucasians were compared using multivariate analysis. A P value < 0.05 was considered significant.

RESULTS

The estimated genotype distributions of the three 5-HT3B receptor SNPs in Indonesians and Caucasians are listed in Table 4.1. The genotype distributions did not deviate from Hardy Weinberg equilibrium.

Table 4.1 Percentages of genotypes in the gene encoding the 5-HT3B receptor in Indonesians and Caucasians

	5-HTRB receptor deletion AAG % (*n* = 349)[#]			5-HTRB receptor 18792A>G % (*n* = 337)[#]			5-HTRB receptor 46698G>A % (*n* = 333)[#]		
	AAG-AAG	del- AAG	del-del	AA	GA	GG	GG	GA	AA
Indonesians	69.5	26.8	3.7	74.7	22.2	3.2	74.1	24.7	1.2
Caucasians	76.8	21.6	1.6	53.1	36.9	10.1	68.4	26.9	4.7

[#] The numbers reflect the number of individuals with successful genotype calls.

Table 4.2 Multivariate analysis of 5HT3B receptor haplotypes and ethnicity

Haplotype	*P* value	Odd ratio (Indonesians vs. Caucasians)	95% confidence interval
AAGAG	< 0.001	1.50	1.18-1.91
deletion AG	0.212	1.49	0.72-2.09
AAGGG	< 0.001	0.58	0.43-0.79
AAGAA	0.181	0.81	0.59-1.13

The haplotypes based on LD pattern of the deletion AAG in 5'-UTR, position 18792A>G in intron position and 46698G>A in 3' near gene position were AAGAA, AAGAG, AAGGG and deletion AG in both the Indonesians and Caucasians. Significant differences of haplotype frequencies between Indonesians and Caucasians were found for the AAGAG and AAGGG haplotypes ($P < 0.05$). The frequency of AAGAG haplotype was significantly higher in Indonesians than in Caucasians (54.7% vs 39.4%). The frequency of the AAGGG haplotype in Caucasians was significantly higher than that in Indonesians (29.3% vs 14.3%).

Based on the multivariate analysis, there were significant differences of the haplotype pairs frequencies between Indonesians and Caucasians ($P = 0.001$) (Table 4.2).

Table 4.3 presents the frequencies of haplotype pairs both in Indonesians and Caucasians. AAGAG-AAGAG had the highest haplotype pair frequency percentage (23.9%) and deletion AG-deletion AG the lowest (2.8%).

Table 4.3 Haplotype pairs' frequencies of the gene encoding the 5-HT3B receptor in Indonesians and Caucasians

Haplotype pair	Indonesians *n* (%)	Caucasians *n* (%)	Total *n* (%)
AAGAG-AAGAG	50 (31.8)	28 (16.6)	78 (23.9)
AAGAG-AAGGG	19 (12.1)	34 (20.1)	53 (16.3)
AAGAG-AAGAA	25 (15.9)	27 (16.0)	52 (16.0)
AAGAG-deletion AG	28 (17.8)	18 (10.7)	46 (14.1)
AAGGG-AAGGG	5 (3.2)	18 (10.7)	23 (7.1)
AAGGG-AAGAA	8 (5.1)	15 (8.9)	23 (7.1)
deletion AG-AAGGG	8 (5.1)	14 (8.3)	22 (6.7)
AAGAA-AAGAA	2 (1.3)	8 (4.7)	10 (3.1)
deletion AG-AAGAA	6 (3.8)	4 (2.4)	10 (3.1)
deletion AG-deletion AG	6 (3.8)	3 (1.8)	9 (2.8)

DISCUSSION

To the best of our knowledge, this is the first study to report the haplotypes frequencies in the *5-HT3B* gene in Asians. The study shows that the frequencies of AAGAG and AAGGG haplotypes in the gene encoding 5-HT3B receptor differ significantly between Indonesians and Caucasians. This finding may be helpful to understand interethnic variation of disease and drug response related to the 5-HT3B receptor.[10] We compared allele frequencies in Indonesian cancer patients and Caucasian healthy subjects. To rule out a disease effect, a comparison with Caucasian cancer patients may have been preferable. However, since the study by Tremblay[9] reported comparable genotype frequencies of the insertion/insertion, insertion/deletion and deletion/deletion genotypes of the -100_-102deletion AAG variant (78.1%, 20.7%, 1.2% respectively) in Caucasian cancer patients as we found in Caucasian healthy subjects (76.8%, 21.6%, 1.6% respectively), an effect of disease on allele frequencies is not very likely. In most pharmacogenetic studies regarding the *5-HT3B* receptor gene, the deletion AAG variant was studied for association with drug response phenotypes. In an in vitro study about the functional characterization of the -100_-102 deletion AAG, it was shown that this variant allele affects the 5-HT3B receptor promoter activity by 25-40%, possibly as a result of interference with mRNA.[11] This finding has led to the establishment of an association between this variant and clinical responses.

For example, a study in Caucasians found that patients with the deletion AAG experienced more frequent vomiting after chemotherapy than patients with the other 5-HT3B genotypes. The study result supported that failure of response to 5-HT3 receptor antagonists, such as ondansetron and tropisetron, was related with this deletion of the *5-HT3B* receptor gene.[9] In a second pharmacogenetic study on paroxetine-induced nausea, it was shown that patients with the deletion AAG had significantly more frequent nausea than patients with the homozygous wild type genotype.[6] Yet, in a third study of the influence of 5-HT3B receptor variants to the occurrence of post operative vomiting (POV), it was found that the 100-102 deletion AAG did not have any significant association with the occurrence of POV. However, these authors showed that another deletion variant, the 201-202 deletion of CA, significantly influenced the POV incidence.[8] Likewise, in our study, the frequency of the deletion AAG and the haplotype including the deletion was not significantly different between Indonesians and Caucasians. However, there were significant differences between the Indonesian and Caucasian population in the distribution of the pairs of haplotypes including the deletion AAG. Thus, differences in 5-HT3B antagonist response between Asians and Caucasians can not be ascribed to differences in the frequency of the deletion AAG but may be attributable to the differences in haplotype pairs that exist in each population. However, the effect of the deletion AAG or its haplotype has never been studied in Asian patients in relation to unresponsiveness to 5-HT3 receptor antagonists.

A limitation of this study is that we used self-reported ethnicity. However, to make a more accurate assessment of ethnicity also the ethnicity of the parents and grandparents were verified.

In conclusion, Indonesian cancer patients have significant different haplotypes distribution of gene encoding the 5-HT3B receptor compared to healthy Caucasians. Since previous studies of Tremblay et al.[8] and Rueffert et al.[9] have suggested that the SNP rs45460698 (deletion AAG in 5'-UTR position) was predictive for the efficacy of tropisetron and ondansetron, we propose that the interethnic differences in 5-HT3B haplotype frequencies could result in interethnic differences of response to 5-HT3 receptor antagonists. However, this hypothesis should be tested in a prospective study.

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5

Translation and validation of EORTC QLQ-C30 into Indonesian version for cancer patients in Indonesia

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ABSTRACT

Objective: Quality of life studies in Indonesia are still uncommon. This research was aimed to validate the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – C30 (EORT QLQ-C30) in an Indonesian version. The standard procedure of forward-backward translation was adhered to in the translation procedures. The validity procedure included reliability, convergent and discriminant validity, known-groups validity, factor analysis and external convergent validity.

Methods: Data were collected from cancer patients in the Oncology Department of Sardjito Hospital, Yogyakarta, Indonesia, who were treated with cisplatin at the dosage ≥ 50 mg/m^2 as monotherapy or in combinations. The Short Form-36 to assess the external convergent validity of our translated questionnaire.

Results: One hundred twenty-eight patients with different cancer diagnoses were recruited in the validation process from March 2009 to November 2009. The internal consistency with values of > 0.70 was observed in the Indonesian version of the EORTC QLQ-C30 scales. All items in the questionnaire met the criteria of convergent and discriminant validity, except for items 5. Both of the EORTC QLQ-C30 and the SF-36 showed that different diagnoses were associated with a similar impact on quality of life. Factor analysis showed that only the role function and social function loaded onto the second factor together. Correlations between the Indonesian versions of both questionnaires were moderate: between 0.18 and 0.48 for the physical, emotional, social, fatigue and pain domains.

Conclusions: The Indonesian version of the EORTC QLQ-C30 can be used as a questionnaire to assess quality of life in Indonesian cancer patients with high-emetogenic treatments.

BACKGROUND

Cancer and the side effects of cancer treatment are often associated with reduced quality of life (QoL).[1] Although advances in cancer treatment could improve the outcome of therapy in cancer patients, such as survival rate and disease-free conditions, patients continue to experience a major impact of cancer and its treatment on numerous physical and psychosocial conditions. This may consequently affect the patients' normal patterns in their social activities, psychosocial and spiritual well-being.[2-4] Combining treatment strategy with QoL assessment, is considered necessary. In modern cancer care, the views of patients are key in cancer treatment and patient reported outcomes assessment is the future trend in cancer therapy. Moreover, QoL assessment is required to consider the impact of cancer treatment on functional and psychosocial health of patients.[2] The researches of instrument development to measure cancer patients' QoL have been developed in many countries and they are published annually.[3]

Several instruments have been developed to assess QoL in cancer patients in past decades.[4] Combinations of generic and disease specific instruments have been applied to define QoL in patients with multipathology. The European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire (EORTC QLQ-C30) has been used internationally in "more than 3,000 studies" as a generic questionnaire among cancer patients. As stated in the paper by Kleijn and colleagues "this questionnaire has been translated into and validated into more than 50 languages".[5]

The EORTC QLQ-C30 and the Medical Outcomes Study Short Form 36 (SF-36) have five domains in common: physical function, mental health/emotional function, social function, vitality/fatigue, and pain. The two questionnaires are often used to discover the convergent validity of the similar constructs between them. A previous study in nonmalignant pain used these questionnaires and demonstrated that both of the questionnaires had acceptable psychometric characteristics.[4]

Information about cancer patients' QoL in the Indonesian population is inadequate. The publications in this field are focused on children. A study about health-related quality of life in childhood with acute lymphoblastic leukemia suggested that the patients and their family should be supported by psychosocial care during the cancer treatments. Psychosocial care during cancer interventions could improve patients' quality of life.[6] Consequently, the area of quality of life research needs to be developed urgently in Indonesia in order that better supportive care during cancer interventions may be proposed.

The limited research on QoL in Indonesia is associated with the unavailability of validated questionnaires in Indonesian versions. Therefore, the objective of this study was to translate and linguistically validate the Indonesian version of the EORTC QLQ-C30 in cancer

patients. In this study, the SF-36 was used as a gold standard to test the external convergent validity of QLQ-C30. The SF-36 questionnaire has been translated into Indonesian version.[7] The reason for using SF-36 as gold standard was that the SF-36 has been used and validated in Indonesian version.[8-12] The Indonesian version of the EORTC QLQ-C30 encompassed translations from the original English versions with forward-backward translation, pilot testing, and review. In order to obtain the Indonesian version of SF-36, the reader can contact the author. The validity procedure includes reliability, multi-factorial analysis, known-groups validity, factor analysis, test-retest validity and external convergent validity.

PATIENTS AND METHODS

Step 1: Translation procedures

The procedures for translation into the Indonesian language were adapted from Koller et al.[13] The translation coordinator contacted two experts in the English Department of two universities independently to do the forward translation of EORTC QLQ-C30. The research coordinator compared the two forward translations and checked them for any discrepancies. The discrepancies between the two translations were discussed with the translators until we agreed on the single provisional forward translation. Modifications were made in this draft to diminish discrepancies and it was adjusted with a view to the habits of Indonesian people. The single forward translation was then back translated by two native speakers of English independently. The English back translations and the original English version were compared with assure that there was no different meaning of the questions in the questionnaires. The discrepancies were discussed and resolved until agreement within the translation group was reached.

Step II: Pilot test

The translated version of the EORTC QLQ-C30 was pilot tested in 20 patients, who were recruited from a university hospital in Yogyakarta, Indonesia. Inclusion criteria for the pilot test were: cancer patients and healthy people; aged 18 years or older; ability to read and write standard Indonesian; and willing to participate in the study. The Indonesian version of EORTC QLQ-C30 was distributed to the patients before their chemotherapy treatment, and to the healthy people. Any difficulties that the patients had experienced with the questionnaire were recorded by the researcher during the time the patients completed the questionnaire. The patients' obstacles in understanding and completing the questionnaires were reviewed and used to modify the questionnaires by the translation group.

Step III: Main study

Subjects

The study population was made up of cancer patients in the Oncology Department of Dr Sardjito Hospital, Yogyakarta, Indonesia, who were treated with a cisplatin dosage ≥ 50 mg/m^2 as monotherapy or in combined chemotherapy regimens. Patients aged ≥ 18 years old with a Karnofsky Index ≥ 50% were included. Exclusion criteria were: patients with the presence of nausea or vomiting 24 hours before chemotherapy; use of other anti-emetics, benzodiazepines or neuroleptics, or the application of radiotherapy within 24 hours before start of chemotherapy and use of opioids within the previous 2 weeks.

We studied patients with cisplatin as subjects because cisplatin is one of the cytotoxic agents which has a severe emetogenic effect and has a significant effect on patients' quality of life. Dr. Sardjito Hospital, Yogyakarta, is a tertiary care public hospital with approximately 750 beds, and 250 beds among them were third class services. Most of the third class patients are supported by government health insurance in public and private hospitals. Nevertheless, there are some third class patients who are not supported by government health insurance. Thus, these patients could not pay to get good services from a private hospital. This is due to the fact that the health services in this hospital are dedicated to poor people.

Data collection

Patient's sociodemographic data such as age, sex, education, diagnoses of cancer and performance status of patients based on Karnofsky Performance Status (KPS) were collected from their medical records. The procedure of the patients' data collection in the main study was done before administration of cytotoxic drugs. After informed consent procedures were completed, patients filled out questionnaires a few hours before chemotherapy and on day 5 after chemotherapy administration at the hospital. The time of administration of the questionnaire was based on a previous study.[9] The study was approved by the local ethics committee of the Medical Faculty, Gadjah Mada University, Yogyakarta.

Statistical analysis

Descriptive data are presented with means and standard deviations (SDs). Discrimination of the instruments was tested by floor and ceiling effects. Large floor and ceiling effects are assumed to show poor discrimination of the instruments.

The internal consistency of each subscale was assessed by using Cronbach's alpha coefficient. It was considered to be acceptable as good internal consistency occurs when Cronbach's

alpha is 0.70 or greater. Multi-trait scaling analysis was used to test the convergent and discriminant validity of the EORTC QLQ-C30. Convergent validity was revealed if the item-domain correlation was ≥ 0.40, while the requirements for discriminant validity were satisfied if the value of correlation coefficients between the item and its own domain was higher than other domains. Known-groups validity was evaluated based on different diagnoses using *T*-test or ANOVA-test. Factor analysis was used to extract factors from 15 indicators of quality of life in EORTC QLQ-C30. Kaiser-Meyer-Olkin (KMO) and Bartlett's Test were tested to know if the data were suitable for factor analysis. The loading criterion was set at less than 0.40 of absolute value. Convergence between instruments (external convergent validity) evaluates correlations between similar domains of the SF-36 and EORTC QLQ-C30. If one domain has a similar underlying construct, it will show a high correlation with the other domain. Pearson's correlation was used to compute construct validity. Correlations above 0.40 are considered satisfactory for convergent validity. However, if this correlation is too high (> 0.70), it can be caused by different concept measurements, or there may be some useful information obtained by including the two domains compared to including only one of the domains. Correlation coefficients of > 0.5, 0.35-0.50 and < 0.35 were considered to represent strong, moderate, and low correlations, respectively. The discriminant validity means that scales measuring different constructs should have a low correlation, i.e., < 0.40.[2-4,14,15]

RESULTS

Step I: Translation and back-translation

In the Indonesian version of SF-36, some questions were adjusted to Indonesians' habits and occupations. For example: moderate activities such as moving a table, using a vacuum cleaner, bowling, or playing golf in item 3b, was translated into "moving a table, cycling and working in the garden", as "using a vacuum cleaner, bowling and playing golf" are not done by most Indonesian people. Another example, in the original version of SF-36, "walking more than one mile" in item 3g, was translated into "walking more than 1.6 kilometers", as Indonesian people use "kilometers". In the first draft of EORTC QLQ-C30, the medical words such as insomnia, constipation and depression were translated into non-medical word such as, difficult to sleep, difficult to defecate and feeling stress.

There were some differences in the back-translations of the questionnaire but the translators were of the opinion that the differences would not change the meaning of word, because the Indonesian language has less vocabulary than the English language. The differences in

expression of the response choices of the Likert-type scales were also present between the back-translation versions and the original version. But the translators were of the opinion that the differences were only about the formal style of the language and would not change the meaning of the expression. Therefore, the expression of the response choices used the less formal style which is appropriate with the lower and middle levels of education in these cancer patients.

Step II: Pilot test

Twenty people (10 healthy people and 10 cancer patients) were enrolled in the pilot test. The age range for the healthy people varied from 19 to 49 years with a mean of 26.10 years (SD = 8.88); the age range of cancer patients varied from 26 to 63 years with a mean of 49.60 years (SD = 9.83). The average completion time of translated version of the EORTC QLQ-C30 were 4.54 min (SD = 1.00) for healthy people and 5.88 min (SD = 1.97) for cancer patients. Most patients were able to fill out the questionnaires by themselves, except for items 29 and 30 in EORTC QLQ-C30, where the patients needed an explanation about the meaning of the quality of life in the less formal language style and about the differences between items 29 and 30. Item 29 in EORTC QLQ-C30 asks the patients to rate their overall health during this past week, whereas item 30 asks the patients to rate their quality of life. Generally, the subjects asked about the meaning of quality of life or asked to the researcher to give a short description about quality of life.

Step III: Main study

Patients' demographic data

One hundred and twenty eight patients were recruited in this study from March 2009 to November 2009. Patients had different diagnoses of cancer. The most prevalent diagnostic category was cervical cancer. Out of 57% cancer patients had KPS of < 90%, which means that more patients needed some efforts to carry on normal activity with some signs or symptoms of cancer than patients with normal activity and minor signs or symptoms of cancer. When we dichotomized the sample on the basis of KPS < 80 and 80-100 (n = 118), we found that the number of patients in the < 80 group was 10 and the number of patients in the 80- 100 group was 118. Furthermore, sensitivity analyses regarding this point by for instance dichotomizing the sample in < or ≥ than 70 on the KPS would run into difficulties as that would imply comparing n = 4 (for KPS < 70) with n = 124 (for KPS ≥ 70). The demographic data of the patients are shown in Table 5.1. In regard to educational status, most of the patients only attended elementary school level. This illustrates the low

educational level experienced by most of the patients in Dr. Sardjito Hospital where the services of this public hospital are dedicated to poor people.

Discrimination and internal consistency

Table 5.2 lists floor and ceiling effects of EORTC QLQ-C30 and SF-36.

The large floor and ceiling effects were found in single items, emotional function and cognitive function of EORTC QLQ-C30 (0.8% to 92.2%). Whereas, the large floor and ceiling effects in SF-36 were seen on physical and emotional roles (11.1% to 76.2%).

The physical and role functions in SF-36 and the pain, fatigue and single items in EORTC QLQ-C30 were questionable following psychometric analysis (mean and SD), i.e., mean: 16.5 and SD: 33.3 in the physical role domain of the SF-36.

Cronbach's alpha coefficients are presented in Table 5.2 for all domains of the two questionnaires. This study found that for the SF-36 values above 0.70 were observed in following domains: physical function, social function, pain, physical role, and emotional role. In EORTC QLQ-C30, those five domains were also valued above 0.70. This finding means that for those five domains, EORTC QLQ-C30 has the same reliability as SF-36.

Table 5.1 Sociodemographic data of the patients

	n	%
Age, years (*n* = 128)		
Mean (SD)	47.6 (10.5)	
Range	22-70	
Sex (*n* = 128)		
Male	9	7.0
Female	119	93.0
Education (*n* = 128)		
No schooling	46	35.9
Elementary school	35	27.3
High school	36	28.1
Undergraduate	7	5.5
Diagnosis of cancer (*n* =128)		
Cervical cancer	77	60.1
Ovarian cancer	35	27.4
Others	16	12.5
KPS		
< 90%	73	57.0
90-100%	55	43.0

SD, standard deviation; KPS, Karnofsky Performance Status.

Table 5.2 Means, floor and ceiling effects, and Cronbach's α coefficients of the domains in the QLQ-C30 and SF-36

Domain	Mean	SD	Floor (%)	Ceiling (%)	Cronbach's α coefficient
QLQ-C30					
Physical function	74.0	21.8	1.6	23.0	0.82
Role function	63.3	24.0	3.2	12.7	0.79
Emotional function	93.5	12.2	0.8	68.3	0.78
Social function	65.8	23.7	0.8	17.5	0.83
Cognitive function	93.8	14.3	0.8	79.4	0.82
Global QoL	58.7	16.4	0.8	2.4	0.80
Pain	34.5	26.5	24.6	3.2	0.85
Fatigue	30.2	21.6	15.1	0.8	0.72
Nausea and vomiting	12.4	21.9	68.3	0.8	0.70
Dyspnea	5.2	18.5	91.3	1.6	Single item
Insomnia	32.4	30.7	39.7	4.0	Single item
Appetite loss	20.0	28.5	60.3	4.0	Single item
Constipation	17.6	27.4	65.1	3.2	Single item
Diarrhea	3.9	15.5	92.1	1.6	Single item
Financial difficulties	42.2	29.6	22.2	7.1	Single item
SF-36					
Physical function	63.9	25.1	1.6	9.5	0.82
Mental health	75.3	18.1	0.8	9.5	0.66
Social function	65.8	23.7	1.6	11.1	0.70
Energy	63.8	18.9	0.8	5.6	0.60
Pain	63.1	29.4	0.8	21.4	0.87
General health	55.3	15.8	0.8	0.8	0.60
Physical role	16.5	33.3	76.2	11.1	0.92
Emotional role	23.2	40.7	73.0	20.6	0.97

QLQ-C30, quality of life core questionnaire; SF-36, Study Short Form 36; QoL, Quality of Life.

Furthermore, in EORTC QLQ-C30 the values above 0.70 were not only observed in those five domains, but also in all domains. We excluded the outlier factor in the cognitive function to get a better value of Cronbach's alpha.

Multi-trait analysis

Table 5.3 shows that the convergent validity was revealed due to all of the value of coefficient correlations between the item and its own domain were ≥ 0.40, except for items 5, 10, 15 and 25. Table 5.3 also shows that all items meet the discriminant validity criterion except for item 5 with the value of 0.38.

Table 5.3 Multi-trait scaling analysis of EORTC QLQ-C30

Item no	Description	PF	RF	EF	CF	SF	FA	NV	PA	QL
1	Strenous activity	-.75	-.41	-.04	-.05	.08	.22	.07	-.01	.03
2	Long walk	-.75	-.32	-.11	-.09	.08	.12	-.03	-.02	.09
3	Short walk	-.69	-.40	-.09	-.11	-.08	.31	.05	.08	.03
4	Stay in bed/chair	-.61	-.30	-.22	-.05	-.03	.43	.17	.15	-.15
5	Needed help in eating/dressing/washing	***-.38***	-.37	-.45*	-.21	-.17	.25	.05	.34	-.13
6	Limited work	-.34	-.65	-.25	-.12	-.35	.25	-.06	.28	.09
7	Limited hobbies	.-30	-.57	-.18	.02	-.27	.31	.13	.28	-.04
21	Tense	-.14	-.17	-.65	-.08	-.25	.14	.10	.25	-.05
22	Worried	-.11	-.17	-.64	-.12	-.25	.16	.06	.21	-.08
23	Irritable	-.15	-.15	-.54	-.05	-.12	.12	.05	.14	-.10
24	Depressed	-.03	-.03	-.49	-.11	-.13	-.12	.01	.13	-.12
20	Concentration	-.10	-.09	-.25	-.58	-.07	-.11	-.01	-.26	-.14
25	Memory	-.08	-.01	-.01	**-.34**	-.18	-.04	-.17	.04	-.04
26	Family life	.28	-.01	-.12	-.12	-.75	-.03	-.01	.05	-.11
27	Social life	-.16	-.33	-.09	-.02	-.71	.17	-.06	.24	.02
10	Need rest	-.14	-.17	-.14	-.10	-.21	**.28**	-.04	.05	-.08
12	Feel weak	-.30	-.27	-.29	-.04	-.19	.40	.03	.29	-.10
18	Tired	-.34	-.26	-.32	-.11	-.17	.50	.14	.31	-.10
14	Nausea	-.08	-.09	-.21	-.02	-.24	-.06	.40	.15	-.15
15	Vomiting	-.05	-.11	-.21	-.09	-.19	.13	**.34**	.14	-.15
9	Pain	-.20	-.27	-.26	-.14	-.07	.16	.09	.59	.07
19	Relation of pain with daily activities	-.29	-.38	-.33	-.19	-.15	.27	.03	.60	-.29
29	Overall physical condition	.07	.06	.23	.03	.14	-.07	-.20	-.05	.62
30	Quality of life	.14	.07	.25	-.07	.03	-.19	-.22	-.19	.65

EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; PF, Physical Function; RF, Role Function; EF, Emotional Function; CF, Cognitive Function; SF, Social Function; FA, Fatigue; NV, Nausea and Vomiting; PA, Pain; QL, Quality of Life.
The bold numbers show that the coefficient correlation between the items and its own domain are ≤ 0.40.
The number with * show that the coefficient correlation between the item and other domain is higher than the coefficient correlation of the item and its own domain. All the values in the boxes are significantly correlated.

Known-groups validity

The known-groups validity of the two questionnaires among three groups of diagnoses is presented in Table 5.4. We measured the five domains between in the EORTC QLQ-C30 questionnaire, that is, physical function, emotional function, social function, pain, and energy/fatigue. There were no significant differences in both EORTC QLQ-C30 when they were applied in different diagnoses of cancer ($P > 0.05$).

Table 5.4 Scores of the five QoL domains of QLQ-C30 in the cancer diagnosis groups

Diagnosis	*n* (%)	PF Mean (SD)	EF Mean (SD)	SF Mean (SD)	FA Mean (SD)	PA Mean (SD)
Cervical cancer	77 (60.1)	72.3 (22.5)	93.9 (11.5)	66.2 (22.5)	31.5 (23.6)	33.9 (26.9)
Ovarian cancer	35 (27.4)	72.7 (21.6)	92.9 (14.5)	68.0 (24.0)	32.2 (19.6)	35.4 (27.9)
Others	16 (12.5)	81.5 (19.9)	90.0 (14.2)	58.2 (27.9)	23.5 (17.1)	40.4 (25.6)
P value*		0.24	0.72	0.46	0.37	0.80

PF, Physical Functioning; EF, Emotional Function; SF, Social Function; FA, Fatigue; PA, Pain.
* One way ANOVA test or Kruskall-Wallis test.

Factor analysis

Based on the KMO and Bartlett test, the data was suitable for factor analysis (KMO value was 0.708 and Bartlett test was 1.765×10^3, $P = 0.000$). The extraction of factors was based on the criterion of an eigenvalue greater than one that is ten-factor solution with 70.41% of total variance.

Factor analysis results are presented in Table 5.5. All items in each domain loaded significantly on one factor of 10 factors. All of the items in physical function, except item 5, loaded significantly on the first factor. The emotional function items loaded significantly on the second factor, except item 23. Pain items loaded significantly on the third factor, role function and social function items on the fourth factor, nausea and vomiting items on fifth factor, general quality of life items on the sixth factor, fatigue items on seventh factor, and cognitive function' items on the eight factor. Item 23 loaded significantly on the ninth factor, and item 5 loaded significantly on the fifth factor.

External convergent validity

The external convergent validity of the questionnaires is presented in Table 5.6. This analysis was performed for physical functioning, social functioning, emotional functioning, fatigue, and pain.

Moderate correlations (0.35 - < 0.5) were observed in the physical function and pain domains, whereas the other functions showed low correlations between the questionnaires ($P < 0.05$). Otherwise all of the discriminant validity in the two questionnaires met the $r < 0.40$ criterion ($P < 0.05$).

Table 5.5 Factor analysis of EORTC QLQ-C30

		Factor									
	Item	1	2	3	4	5	6	7	8	9	10
PF	Strenous activity	.833	.016	-.021	.225	-.169	.018	.092	-.075	-.051	-.008
	Long walk	.832	.075	.068	.062	-.131	-.093	.085	.011	.089	-.100
	Short walk	.790	.053	.116	.199	.064	.004	.028	-.048	-.078	.025
	Stay in bed/chair	.668	-.095	.033	.187	.193	.233	.194	.064	.109	.184
	Need help with eating/dressing/washing	**.324**	.220	.097	.169	.463	.017	-.020	.120	.049	.020
RF	Limitation of work or other daily activities	.307	.166	.216	.747	-.004	-.031	.052	.044	.100	.031
	Limitation of hobbies	.288	.186	.049	.737	.134	.169	-.019	-.051	-.107	.115
EF	Tense	.009	.892	.159	.183	.144	.027	.060	-.107	.080	.008
	Worried	.003	.891	.138	.141	.101	.104	.076	.045	.107	-.044
	Irritable	.228	**.307**	.156	-.103	.256	.082	-.019	.275	.517	.344
	Depressed	.080	.538	.054	-.140	.391	.216	.173	.335	.030	.070
CF	Concentration	.034	.323	.248	-.101	.144	.018	.076	**.399**	-.383	.095
	Memory	-.099	-.022	-.002	.084	-.140	.021	.051	.805	-.095	.024
SF	Family life	-.490	.209	-.055	**.403**	.054	.038	.005	.436	.267	-.148
	Social life	.095	-.007	-.007	.719	.152	-.111	.314	.040	.066	.005
QL	Overall physical condition	-.025	-.097	-.119	-.022	-.109	-.855	-.042	-.189	-.067	.034
	Overall QoL	-.012	-.091	-.142	-.002	-.092	-.867	-.177	.149	.004	-.095
FA	Need rest	.185	-.164	.223	.370	.221	.236	**.160**	.223	.141	-.040
	Felt weak	.284	.017	.252	.144	.229	.108	.707	.063	.107	.077
	18	.297	.133	.178	.147	.204	.156	.748	.041	-.046	.095
NV	Nausea	-.150	.104	.027	.077	.654	.180	.390	-.175	.043	-.097
	Vomiting	-.120	.141	-.009	.131	.793	.073	.055	-.060	-.063	.045
PA	Pain	.054	.080	.753	.150	.133	.103	.221	-.035	-.024	.083
	Pain interfered with daily activities	.133	.194	.771	.226	.007	-.055	.210	-.063	-0.01	.158

PF, Physical Function; RF, Role Function; EF, Emotional Function; CG, Cognitive Function; SF, Social Function; QL, Quality of Life; FA, Fatigue; NV, Nausea Vomiting; PA, Pain. The bold numbers show that the absolute values for loading factor are less than 0.40. All the numbers in the boxes have significant values.

Table 5.6 Pearson's correlation coefficient among the subscales in the Standard Indonesian version of SF-36 and QLQ-C30

		SF-36 PF	SF-36 MH	SF-36 SF	SF-36 E	SF-36 PA
QLQ-C30	PF	**0.40**	-0.03	0.33	0.21	0.28
QLQ-C30	EF	0.05	**0.25**	0.20	0.28	0.25
QLQ-C30	SF	0.04	0.07	**0.11**	0.16	-0.02
QLQ-C30	FA	-0.28	0.11	0.36	**-0.17**	-0.27
QLQ-C30	PA	-0.20	-0.20	-0.16	0.27	**-0.45**

PF, Physical Functioning; MH, Mental Health; EF, Emotional Function; SF, Social Function; E, Energy; FA, Fatigue; PA, Pain. The bold numbers show the significant Pearson's correlation coefficients between the same subscales of the SF-36 and the QLQ-C30.

DISCUSSION

This study showed the acceptable psychometric properties of reliability and validity evaluation of EORTC QLQ-C30 in our Indonesian version. This scale development will help clinicians to describe the human side of cancer treatment in Indonesia. The practicing oncologist can benefit greatly from the work that was performed in developing and validating this scale, by applying the instrument to the selection of treatment modalities based on both treatment efficacy and the patient's wishes. In the future, QoL research in Indonesia will continue to be integrated into the practice of oncology.

The translation of EORTC QLQ-C30 into the Indonesian language was in compliance with the procedures developed by the EORTC Quality of Life Study Group.[13] The backward translation of the modified items was compared with the original versions and was found to be satisfactory. In the pilot study, the cancer patients were able to complete the questionnaire in a somewhat longer time than the healthy subjects. This could be due to the severity of the diseases which made the patients need more time to focus on completing the questionnaires. The patients' cognitive function in understanding the questionnaires, could be affected by multiple and severe symptoms in cancer.[16] Nevertheless, all of the patients in pilot testing were able to fill in the questionnaire by themselves.

Discrimination in physical function, role function, social function, global quality of life, pain and fatigue in EORTC QLQ-C30 were good (i.e., 0.8% for floor effects and 17.5% for ceiling effects in social function). However, in the single items, emotional and cognitive function showed poor discrimination (i.e., 4.0% for floor effects and 60.3% for ceiling effects in appetite loss). The poor discriminations could be related to the mean and SDs

value of the domains. All of the functions in SF-36 showed good discrimination, except for physical role and emotional role. Poor ability of patients to distinguish the physical and emotional role or the narrow response of these domains could give rise to this poor discrimination. All functions with poor discrimination had less than clear descriptions of cancer patients' feelings.

Poor discrimination and cancer patients' feeling could be affected by anxiety and depression during chemotherapy. Anxiety and depression may result from excessive feelings of distress. This psychological distress had significant association with memory and concentration.[17] Indeed, the small sample size could effect the poor discrimination. For example in the nausea symptoms, there were 109 patients who answered "not at all", and the other patients answered the other responses. It showed that the patients' responses were not distributed normally in all of the responses. Thus, the floor effect was shown by nausea symptom. A larger sample size could result in better distribution responses. Therefore, the interpretation of this scale in a broad spectrum of cancer patients must be careful and might need to be validated when applying it to other types of cancer. This phenomenon may contribute significantly to poor discrimination and descriptive assessments. Ideally, the questionnaires should be given 72 hours before the administration of the chemotherapy.[9] However, the system in this hospital could not trace the patients 2-3 days before administration of chemotherapy. As a result, the questionnaires were given only a few hours before chemotherapy. Patients' memory and concentration levels a few hours before chemotherapy could be affected by patients' psychological distress.

Another possible explanation of these results is that certain symptoms (dyspnea, insomnia, appetite loss, constipation and diarrhea) were not experienced by the patients, or that these symptoms were experienced by the patients but the patients could cope despite these symptoms.

In the SF-36 questionnaires, the internal consistency was somewhat problematic for mental health, energy and general health. The low to middle education level of the subjects could have affected the internal consistency: the subjects needed more explanation about the response options. The Cronbach's α of EORTC QLQ-C30 was acceptable in all scales.

The convergent and discriminant validity of EORTC QLQ-C30 were consistent with the results of previous studies. The EORTC QLQ-C30 in simplified Chinese version and in Korean cancer patients also met the convergent and discriminant validity.[3,18] The low coefficient correlation in item 5, 15, 20 and 25 may be caused by the skewed distribution of the responses. Out of 93% patients answered "not at all" response for item 5, only 4.7 %

of patients answered "very much" for item 10, 93.8% and 91.4% of patients also answered "not at all" for item 20 and 25. The previous study in Korean cancer patients also reported the same problem.[18]

In order to examine an additional issue of the psychometric characteristics of the Indonesian version of the EORTC QLQ-C30 questionnaire, it was decided to compute known-groups validity. The known-groups validity analyses which were performed using different diagnoses of cancer showed that there were no statistically significant differences among groups. This fact explained that all of the domains in EORTC QLQ-C30 were not better in discriminating ovarian, cervical and other diagnoses of cancer. We acknowledge that this is just one phase in addressing this issue. Further study should include additional questionnaires from samples with varying diagnostic categories of cancer.

The factor analysis showed the satisfactory result that all items in each domain loaded on one factor. Only role function and social function loaded on the second factor together. This factor described the effect of limited role to social life.

The external convergent validity correlation between domain of SF-36 and EORTC QLQ-C30 values was under 0.70. Physical function and pain had strong correlations in both questionnaires. However, the moderate and low correlation coefficient in the other domains of SF-36 and EORTC QLQ-C30 suggest that the subscales were assessing distinct components of the construct of quality of life. The differences can be explained in the physical function of the SF-36 which contains 10 items, while the EORTC QLQ-C30 only contains five items. In some items SF-36 has more specific questions than EORTC QLQ-C30. Nevertheless, the EORTC QLQ-C30 has a broader spectrum of symptoms, such as nausea/vomiting, pain, insomnia, dyspnea, appetite loss, constipation and diarrhea.

The patients had difficulties in completing the questions number 29 and 30 in EORTC QLQ-C30. Therefore the instructions of number 29 and 30 were modified to facilitate the patients' understanding. We also gave some explanations to the patients related to question number 29 and 30. Another study in China also modified the questions number 29 and 30 in EORTC QLQ-C30 to increase the patients' understanding.[2] The translation procedures of previous studies on EORTC QLQ-C30 in Turkish and Moroccan minority ethnic groups in the Netherlands suggested that the "questionnaire was produced for oral administration and needed some modifications because of the high illiteracy in Moroccans' first generation in Netherlands". The subjects in this study also need additional information about the meaning of "quality" word.[19] Results of our study were consistent with the two previous studies, especially in the short description of questions number 29 and 30, also in the description of the word "quality".

The high internal consistency of EORTC QLQ-C30 is also consistent with a previous study in patients with chronic nonmalignant pain. Generally, the Cronbach's α values observed in this study are higher than those in the patients with chronic nonmalignant pain.[4] The low Cronbach's α value for cognitive function was also found in the previous study with various diagnoses of cancer; also homogenous diagnoses of cancer.[20,21] Otherwise, the other studies in China and Singapore had a lower internal consistency (< 0.70) for physical function and cognitive function in various diagnoses of cancer.[2,15] The finding in our study was consistent across different cultures.

The known-groups validity of the EORTC QLQ-C30 is different from a previous study which compared the same instruments. The emotional function, social function and pain were significantly different between EORTC QLQ-C30 and SF-36 in the previous study.[4] Future research on this issue is called for.

Factor analysis results of this present study were not consistent with the factor analysis of EORTC QLQ-C30 in Korean cancer patients, which showed two factors with more than one domain loaded. The "emotional distress" factor was appear because the emotional function and cognitive function were loading together in one factor.[18] The variability of cancer diagnoses, patients' supportive care and patients' condition during they filled in the questionnaire may cause different result of factor analysis among the countries.

The result of convergent validity is also consistent with two previous studies in cancer patients, where the convergent validity coefficient values ranged from 0.47-0.74 and 0.40 to 0.68.[22,23] Conversely, the study in cancer patients with chronic pain showed that the coefficients values ranged from 0.70 to 0.80.[4] The correlation coefficients of pain symptoms in cancer diagnoses were lower than those in chronic non-malignant pain patients. This finding illustrates that the pain level in cancer diagnoses is less important than those of chronic non malignant pain. The other symptoms could have important impacts on QoL, such as nausea and vomiting. Otherwise, the correlation coefficients between mental and physical function, energy and mental function in cancer patients were higher than those in chronic non malignant pain patients. Results showed that the correlation of physical and mental functioning in cancer patients is more important than the coefficient correlation of physical and mental function in chronic non-malignant pain. Another study in Germany indicated that patients had different interpretations of health subscales of EORTC QLQ-C30, SF-36 and Functional Living Index Cancer Questionnaire (FLIC), even though all three questionnaires had convergent validity in physical function, emotional function, pain, fatigue and nausea/vomiting. These results were caused by the different views of QoL in three questionnaires.[23]

The convergent validity in our study was consistent with another study of questionnaire validation which was done in Indonesia between Nepean Dyspepsia Index (NDI) and SF-36. This research also showed low and moderate correlation between the functions in both questionnaires (0.036-0.638) with $P < 0.05$.[8]

A limitation of our study is the relatively small and unequal sample size in each disease group. Even though the sample size was small and unequal, we believe that this study is still valid and relevant, because all of the domains in the EORTC QLQ-C30 were reliable and met the convergent validity, construct validity and test-retest validity. We also supported the validation analysis with factor analysis which showed that every domain in the EORTC QLQ-C30 loaded significantly on one factor. A larger sample size of patients with each type of cancer will facilitate conclusions on how different types of cancer may affect patients' responses to the questionnaires.

The result of this scale development process could be applied to hospitalized patient. Moreover, the scale that we developed may be limited to those patients treated with cisplatin. For the time being, our study results will be used in future to study QoL only for high-emetogenic cancer treatment. At the same time, we would like to point out that the sample size in our study as such is not uncommon in related research.

Conclusion

In conclusion, this study provides an Indonesian version of the EORTC QLQ-C30 and SF-36 questionnaires. Despite the fact that overall psychometric properties of both instruments were acceptable, this study indicates the further development of the instruments in an Indonesian version is required to achieve ideal tools to measure psychometric properties. The results of the present study should be confirmed in a study with an increased sample sizes.

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APPENDIX

Indonesian version of EORTC QLQ-C30

Kami ingin mengetahui beberapa hal yang berkaitan dengan Anda dan kesehatan Anda. Jawablah semua pertanyaan dengan melingkari angka yang paling sesuai. Tidak ada jawaban "salah" atau "benar". Informasi yang Anda berikan akan dirahasiakan.

		Tidak	Sedikit	Sering	Sangat Sering
1	Apakah Anda mengalami kesulitan saat melakukan kegiatan yang berat, seperti membawa barang belanjaan atau koper yang berat?	1	2	3	4
2	Apakah Anda mengalami kesulitan jika berjalan kaki dalam jarak yang jauh?	1	2	3	4
3	Apakah Anda mengalami kesulitan saat berjalan kaki meskipun dalam jarak yang pendek, misalnya di sekitar rumah Anda?	1	2	3	4
4	Apakah setiap hari Anda harus berbaring di tempat tidur atau duduk di kursi ?	1	2	3	4
5	Apakah Anda memerlukan bantuan orang lain saat makan, berpakaian, mandi atau buang air?	1	2	3	4
	Dalam seminggu terakhir:	**Tidak**	**Sedikit**	**Sering**	**Sangat Sering**
6	Apakah Anda mengalami keterbatasan saat bekerja atau melakukan kegiatan sehari-hari lainnya,?	1	2	3	4
7	Apakah Anda mengalami keterbatasan saat melakukan kegiatan santai atau kegiatan yang merupakan hobi Anda?	1	2	3	4

	Dalam seminggu terakhir:	Tidak	Sedikit	Sering	Sangat Sering
8	Apakah Anda merasa sesak nafas?	1	2	3	4
9	Apakah Anda merasa nyeri?	1	2	3	4
10	Apakah Anda perlu beristirahat?	1	2	3	4
11	Apakah Anda sulit tidur?	1	2	3	4
12	Apakah Anda merasakan badan Anda lemah?	1	2	3	4
13	Apakah Anda kehilangan nafsu makan?	1	2	3	4
14	Apakah Anda merasa mual?	1	2	3	4
15	Apakah Anda muntah?	1	2	3	4
16	Apakah Anda sulit buang air besar?	1	2	3	4
17	Apakah Anda diare?	1	2	3	4
18	Apakah Anda kelelahan?	1	2	3	4
19	Apakah nyeri yang dirasakan mengganggu aktivitas Anda sehari-hari?	1	2	3	4
20	Apakah Anda sulit berkonsentrasi pada sesuatu hal, seperti membaca koran atau menonton televisi?	1	2	3	4
21	Apakah Anda merasa tegang?	1	2	3	4
22	Apakah Anda merasa khawatir?	1	2	3	4
23	Apakah Anda merasa mudah tersinggung?	1	2	3	4
24	Apakah Anda merasa depresi?	1	2	3	4
25	Apakah Anda mengalami kesulitan untuk mengingat sesuatu?	1	2	3	4

	Dalam seminggu terakhir:	Tidak	Sedikit	Sering	Sangat Sering
26	Apakah kehidupan keluarga Anda terganggu oleh kondisi fisik atau terapi medis yang Anda jalani?	1	2	3	4
27	Apakah aktivitas sosial Anda terganggu oleh kondisi fisik atau terapi medis yang Anda jalani?	1	2	3	4
28	Apakah Anda mengalami kesulitan keuangan akibat kondisi fisik atau terapi medis yang dialani?	1	2	3	4

Untuk pertanyaan-pertanyaan berikut ini, lingkari angka yang paling sesuai.

29 Bagaimanakah Anda menilai kondisi kesehatan Anda secara keseluruhan selama seminggu yang lalu?

1	2	3	4	5	6	7
Sangat buruk						Sangat baik

30 Bagamanakah Anda menilai kualitas hidup Anda selama seminggu yang lalu?

1	2	3	4	5	6	7
Sangat buruk						Sangat baik

6

Impact of chemotherapy induced nausea and vomiting on quality of life in Indonesian patients with gynecological cancer

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ABSTRACT

Background: Quality of Life (QoL) has become a major outcome in the treatment of patients with cancer. This study is aimed at examining the impact of chemotherapy-induced nausea and vomiting on QoL of patients with gynecological cancer in Indonesia.

Methods: . Chemotherapy-naive patients with gynecological cancer, who were treated with cisplatin at a dosage ≥ 50 mg/m^2 as monotherapy or as part of combination chemotherapy regimens, were recruited in the Oncology Department, Dr. Sardjito Hospital, Yogyakarta, Indonesia. QoL was assessed by using the Indonesian version of EORTC QLQ-C30 and SF-36, administered immediately before and on day 5 after chemotherapy administration. Patients used a daily diary to record nausea and vomiting over 5 days after chemotherapy.

Results: Most (74.9%) of the 179 patients experienced delayed emesis during the 5 days after chemotherapy despite prophylactic use of antiemetics. The delayed nausea and emesis caused significant negative impact on patients' QoL. Nausea in the delayed phase caused negative effects on patients' QoL.

Conclusion: Patients reported negative impact on QoL of delayed emesis after chemotherapy. Poor prophylaxis of patients' nausea and vomiting after chemotherapy interferes with patients' QoL. Medical and behavioral interventions may help to alleviate the negative consequences of chemotherapeutic treatment in patients with gynecological cancers treated with suboptimal antiemetics.

INTRODUCTION

In recent decades, quality of life (QoL) has increasingly become an important outcome in the treatment of patients with cancer. In QoL research, the impact of the illness itself and the cancer treatments are assessed from the patients' perspective. One of the factors most seriously impacting patients' QoL during cancer treatment is chemotherapy-induced nausea and vomiting (CINV), especially when it is inadequately treated by antiemetic drugs.[1] Patients may experience acute or delayed CINV during cancer treatment. Acute CINV is defined as nausea and vomiting episodes which persist during the first 24 hours after chemotherapy administration.[2] Delayed CINV starts after the first 24 hours following chemotherapeutic treatment and may persist up to 120 hours.[3] Patients who experience both acute and delayed CINV have worse QoL compared with patients with delayed CINV only, or without acute and delayed CINV.[1] By using an appropriate prophylactic antiemetic regimen, the incidence of CINV can be substantially reduced. However, despite the availability of highly effective antiemetic drugs, about 20-30% of the patients treated with highly emetogenic regimens still experience nausea and vomiting. This is caused by the presence of some risk factors, such as gender, age and individual susceptibility.[4] Health professionals often underestimate the incidence and prevalence of CINV.[5]

Most gynecological cancer types are treated with highly emetogenic chemotherapeutics, such as cisplatin, carboplatin, paclitaxel and cyclophosphamid when paclitaxel is not available.[6] These drugs are reported to cause emesis in more than 90% of patients without prophylactic use of antiemetics[7] and may seriously impact QoL. In addition to CINV, the psychological distress after cancer diagnosis, especially issues concerning femininity, body image, sexuality and reproduction also have been demonstrated to result in a decrease of the patients' QoL.[5,8]

The incidence of cervical cancer in Indonesia is 13.7 per 100,000 women.[9] Despite this high incidence, information about the patients' QoL is still very limited. Therefore, we undertook this study to assess the QoL in gynecological cancer patients after treatment with highly emetogenic chemotherapeutics, using the European Organization for Research and Treatment (EORTC) for Cancer of Quality of Life Questionnaire (EORTC QLQ-C30) as a disease specific instrument and the Short Form-36 questionnaire (SF-36) as a generic instrument for QOL or functional status. Patients' QoL baseline condition was also determined to know the change of patients' QoL after treatment with chemotherapeutics. In addition, we addressed the impact of delayed CINV on these patients' QoL.

PATIENTS AND METHODS

Patients

The study sample consisted of chemotherapy-naive patients with cervical cancer (n = 120), ovarian cancer (n = 51), uterine cancer (n = 8) and vulvar cancer (n = 7) in the Oncology Department of Dr. Sardjito Hospital, Yogyakarta, Indonesia. They were treated with cisplatin at a dosage ≥ 50 mg/m^2 as monotherapy or in combination chemotherapy regimens. Patients with all diagnoses of gynecological cancer and limited to pelvic or advanced stage of cancer were allowed to be included. Patients were referred by the general practitioners to the Dr. Sardjito hospital, Yogyakarta after the diagnosis was made. The staging procedures consisted of physical examination by a gynecologist and limited imaging when appropriate. Patients in the surgery consideration were treated according to the medical standard in Indonesia.

According to the standard of prophylactic antiemetic drug in the hospital, all patients were treated in the outpatient clinic by 8 mg intravenous ondansetron, and 8 mg intravenous dexamethasone 1 hour before cisplatin administration as a prophylactic antiemetic regimen. All patients were also given oral metoclopramide 10 mg, three times a day, from day 2 to day 5, to prevent delayed emesis.

Patients aged ≥ 18 years old with a Karnofsky Index ≥ 50% were included. Patients with nausea or vomiting 24 hours before chemotherapy, use of other antiemetics than ondansetron and dexamethasone, use of benzodiazepines or neuroleptics, treatment with radiotherapy within 24 hours before the start of chemotherapy and the use of opioids within the previous 2 weeks were excluded.

Patients' socio-demographic data were determined from their medical records. All patients gave informed consent. Data collection on demographics and baseline conditions was completed before administration of the chemotherapeutic drugs. Patients filled out the questionnaires EORTC QLQ-C30 and SF-36 one to four hours before chemotherapy, and on day 5 after chemotherapy administration at the hospital. Not all of the patients could fill in the questionnaires by themselves, and needed researcher assistance to explain some questions, i.e. the questions about general health and general QoL in EORTC QLQ-C30. Patients were also asked to fill in a daily diary record to score the degree of nausea and the vomiting frequency during the 4 days after chemotherapy. The study was approved by the local ethics committee of the Medical Faculty, Universitas Gadjah Mada, Yogyakarta.

Measurements

EORTC QLQ-C30

We used the EORTC QLQ-C30 questionnaire which is available in a validated Indonesian translation.[10] This original questionnaire was developed by the EORTC for patients with all cancer types. The EORTC QLQ-C30 covers basic important personal dimensions in cancer patients, in the physical, psychological and social domains. Furthermore, this questionnaire also covers cancer symptoms or cancer treatment related symptoms such as nausea, vomiting, dyspnea, appetite loss, diarrhea, constipation, insomnia as well as financial impact. The questionnaire has been used extensively in many countries to assess QoL of cancer in patients in their respective countries.[11] The normative data of Dutch population in female subjects was used as reference group (n = 796).[12] We used the Dutch population as the normative data in this study because the normative data of EORTC QLQ-C30 in Indonesian population are not available. The characteristics of Dutch subjects who filled in EORTC QLQ-C30 questionnaire were female respondents (n = 796) and the mean of aged (± SD) was 50.8 ± 15. Around 63% subjects reported the health problems as follow; heart disease, hypertension, asthma/chronic obstructive pulmonary disease, diabetes, depression and joint disease.

SF-36

The SF-36 is a generic instrument which can, therefore, be used in the general population and any group of patients with any illness as a generic QoL-instrument.[13] The SF-36 has QoL-dimensions similar to the EORTC QLQ-C30, that is, physical, emotional/mental, social, pain, and vitality/energy. In previous studies which compared the SF-36 and EORTC QLQ-C30 in patients with cancer, they were found to be satisfactory psychometric instruments in assessing consequences of cancer on the physical, emotional, social, pain, and energy dimensions of the questionnaire.[14] The normative data from Dutch population with age of 45-54 years old was used as reference data in this study (n = 180).[15] We used the Dutch population as the reference because of the collaboration study between the institutions in Indonesia and Netherlands and the normative data of SF-36 in Indonesia population are not available.

Delayed emesis

Delayed emesis was defined as delayed nausea and vomiting, as had to be reported by the patients in their diaries. Delayed nausea was measured by the Nausea Visual Analog Scale (NVAS) using a severity nausea scale of 0-100.[16] Zero on the scale represents 'no nausea' and a higher score represents 'more severe delayed nausea'. Patients were asked to

indicate the number on the NVAS once daily, over a 4 days period after chemotherapy. The frequency of delayed vomiting was defined by asking patients to fill in a daily diary record of vomiting frequency. The vomiting episode was defined as single vomiting, and the next vomiting episode was defined one minute after the previous vomiting episode.[16] The delayed emesis was dichotomized into "response" and "no response" based on patient's daily diary record. Patients were grouped into "response" if they did not experience nausea on 0 to 25 scores and did not vomit during 4 days after chemotherapy. Patients were grouped into "no response" if they experienced nausea and vomiting during the 4 days after chemotherapy.[16]

Statistical analysis

Raw QoL-scores were transformed into function scales which ranging from 0-100. On the EORTC QLQ-C30, higher scales scores on the dimensions indicate better function, i.e. better QoL. Higher scores in symptoms indicate more severe symptoms, i.e. lower QoL. Symptoms scores are assessed with the EORTC QLQ-C30, while dimension scores of the functioning are measured with both EORTC QLQ-C30 and SF-36. Higher scores on the SF-36 indicate better QoL, except for fatigue and bodily pain where higher scores indicate more severe symptoms.

Descriptive data are presented as means and standard deviations (SDs). The differences of patients' QoL before and after chemotherapeutic treatment were analyzed using Student's *T*-test. The differences in functions and scales between the two groups of delayed emesis were defined by independent *T*-test. $P < 0.05$ was considered statistically significant.

RESULTS

Patient characteristics are summarized in Table 6.1. Of the 186 female cancer patients, 64.5% had cervical cancer, 27.4% had ovarian cancer, 4.3% had uterine cancer and 3.8% patients were diagnosed with vulva cancer. The mean age of patients was 48.3 ± 19.8 years. Most of the patients had graduated from high school (34.4%) while 32.3% of patients did not have formal education. Comorbidity was present in 15.6% of patients with one disease and 0.5% of patients with two diseases.

The available cytostatic for the patients in this hospital were cisplatin, cyclophosphamid, doxorubicin and 5FU. In the cervical cancer group, most of the patients who had limited pelvic cervical cancer (73.3%) were treated with cisplatin as single agent or in combination with 5-fluorouracil, although this is not a standard schedule. The dose of cisplatin as single agent was 70 mg/m^2 every 3 weeks, while the dose of cisplatin was 50 mg/m^2 in

Table 6.1 Patient characteristics

Patients characteristics		
Age (*n* = 181)	48.3 (mean)	19.8 (SD)
Education (*n* = 181)	Number	%
No education	60	32.3
Elementary school	50	26.9
High school	64	34.4
Bachelor/Diploma	12	6.5
Type of gynaecological cancer (*n* = 186)	Number	%
Cervical cancer	120	64.5
Ovarian cancer	51	27.4
Uterine cancer	8	4.3
Vulva cancer	7	3.8
Comorbidity (*n* = 186)	Number	%
None	156	83.9
1 disease	29	15.6
2 diseases	1	0.5
Stage of cervical cancer (*n* = 120)	Number	%
Limited to pelvic	88	73.3
Advanced stage	32	26.7
Stage of ovarian cancer (*n* = 50*)	Number	%
Limited to pelvic	31	62.0
Advanced stage	19	38.0
Stage of uterine cancer (*n* = 13*)	Number	%
Limited to pelvic	2	25.0
Advanced stage	3	37.0
Stage of vulva cancer	Number	%
Limited to pelvic	1	14.3
Advanced stage	6	85.7

* Missing data lead to some minor differences in some of the categories.

combination with 500 mg/m^2 of 5-fluorouracil every week. In the ovarian cancer group limited stage (62.0%) the treatment consisted of 500 mg/m^2 of cyclophosphamide, 50 mg/m^2 of adriamycin and 50 mg/m^2 of cisplatin every 3 weeks.

The baseline QoL scores of all subjects are listed in Table 6.2. We compared the baseline QoL in this data with the reference studies.[12,15] For this comparison, we have relied on a publication,[12] for which the raw data were not available for us. As a result is was not possible to adjust this comparison for confounding factors with a multivariate analysis. In the EORTC QLQ-C30, the functions score of this present study in both of the questionnaires were lower than those in reference studies, except for emotional function and cognitive function. Meanwhile, the symptoms scores such as pain, fatigue, nausea and vomiting, sleeping difficulty, appetite loss and constipation were higher than those of reference studies.

Table 6.2 Comparison of baseline patients' quality of life in this study and the reference studies

	Baseline of this study (Mean ± SD)	Baseline of the reference data (Mean ± SD) [12;15]	*P* value
EORTC QLQ-C30	*n* = 186	*n* = 796	
General QoL	60 ± 15	77 ± 18	**< 0.001**
Physical function	77 ± 20	89 ± 17	**< 0.001**
Role function	68 ± 25	87 ± 22	**< 0.001**
Emotional function	94 ± 12	88 ± 17	**0.004**
Cognitive function	95 ± 10	92 ± 16	**< 0.001**
Social function	72 ± 23	93 ± 18	**< 0.001**
Pain	33 ± 25	18 ± 24	**< 0.001**
Fatigue	25 ± 21	20 ± 21	**< 0.005**
Nausea vomiting	5 ± 13	3.9 ± 13	0.300
Dyspnea	5 ± 14	7.6 ± 18	**< 0.001**
Sleeping difficulty	32 ± 30	17 ± 26	**< 0.001**
Appetite loss	18 ± 25	4.4 ± 14	**< 0.001**
Constipation	13 ± 24	6.5 ± 17	**< 0.001**
Diarrhea	4 ± 26	3.8 ± 14	0.942
Financial difficulty	48 ± 48	3.6 ± 13	**< 0.001**
SF-36	*n* = 186	*n* = 180	
General health perceptions	52.9 ± 15.2	71.6 ± 23.0	**< 0.001**
Physical function	51.1 ± 30.6	79.9 ± 24.7	**< 0.001**
Physical role functioning	30.0 ± 40.9	78.9 ± 37.0	**< 0.001**
Emotional role functioning	32.8 ± 43.5	83.6 ± 33.1	**< 0.001**
Mental health	63.2 ± 22.8	76.7 ± 19.6	**< 0.001**
Social function	54.1 ± 22.0	86.1 ± 21.8	**< 0.001**
Bodily pain	58.2 ± 27.5	80.5 ± 26.7	**< 0.001**
Fatigue	61.2 ± 18.9	67.5 ± 20.3	**0.002**
Health change	42.8 ± 28.7	51.9 ± 19.8	**< 0.001**

Values are means (SD). The bold *P* values show the significant differences of baseline QoL scores between this study and the reference studies.

The significant differences of function scores were shown by all functions and symptoms, except for emotional function, nausea and vomiting and diarrhea ($P < 0.001$). Moreover, the Indonesian cancer patients faced higher financial difficulty than the Dutch population. In the SF-36, the Indonesian cancer patients showed significantly lower functions and symptoms than those of reference study ($P < 0.05$).

Seven patients died in this study during the delayed phase, due to their cancer. Most patients (74.9%) experienced delayed emesis in the 4 days following chemotherapy, that is, a response to the attempt to prevent nausea and vomiting. The patients' functions in the baseline and post chemotherapy based on the patients' response are presented in Figure 6.1. At baseline, no significant differences between the response group and no response groups were found for any of the QoL domains and symptoms scale.

On the EORTC QLQ-C30, the patients' functions did not change much or even deteriorated after the chemotherapy. Fatigue was experienced by both response group and no response group patients (Figure 6.1). Meanwhile, in the SF-36, general health perceptions, emotional function and social function were improved after chemotherapy. Figure 6.2 shows the patients' symptoms at baseline and post chemotherapy based on the response and no response groups. This figure shows that the non-response patients experienced more severe dyspnea, sleeping difficulty, appetite loss, and constipation after chemotherapy than at baseline.

The impact of delayed emesis on QoL dimensions in patients with and those without a response is presented in Table 6.3. Significant differences between the two groups in

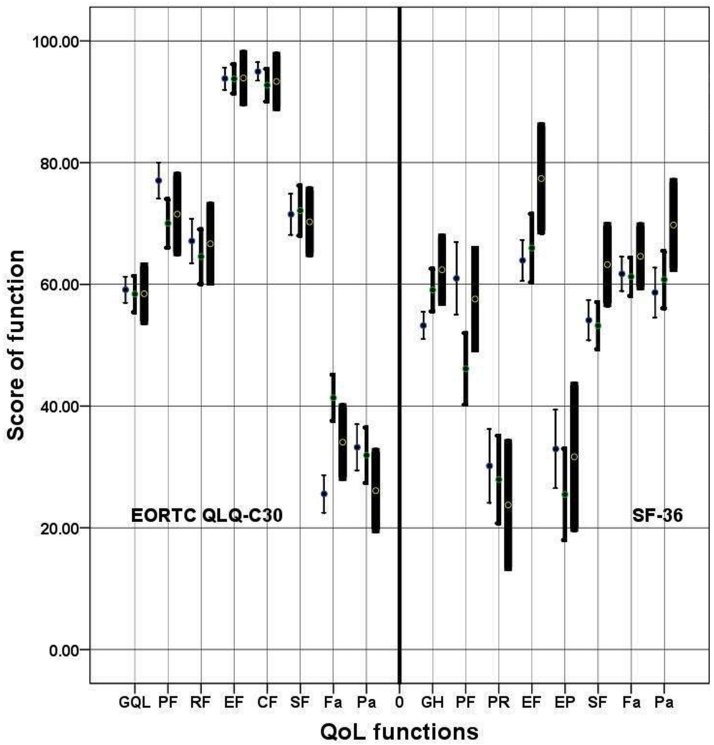

Figure 6.1 Patients' scores on the EORTC QLQ-C30 and SF-36 at baseline and post-chemotherapy in responders and non-responders. GQL, General QoL; PF, Physical Function; RF, Role Function; EF, Emotional Function; CF, Cognitive Function; SF, Social Function; Fa, Fatigue; Pa, Pain; GH, General Health; PR, Physical Role; EP, Emotional Problem.

Group:
Baseline
Post chemotherapy-no response
Post chemotherapy-response group

symptoms, such as fatigue, nausea, vomiting, and appetite loss were found on the EORTC QLQ-C30 questionnaire. The "no response" patients experienced more severe symptoms than "response" patients in whom the attempted prevention of nausea and vomiting was effective, according to the diary data. Significant differences between the two groups on QoL dimensions, such as physical function, mental function, social function and bodily

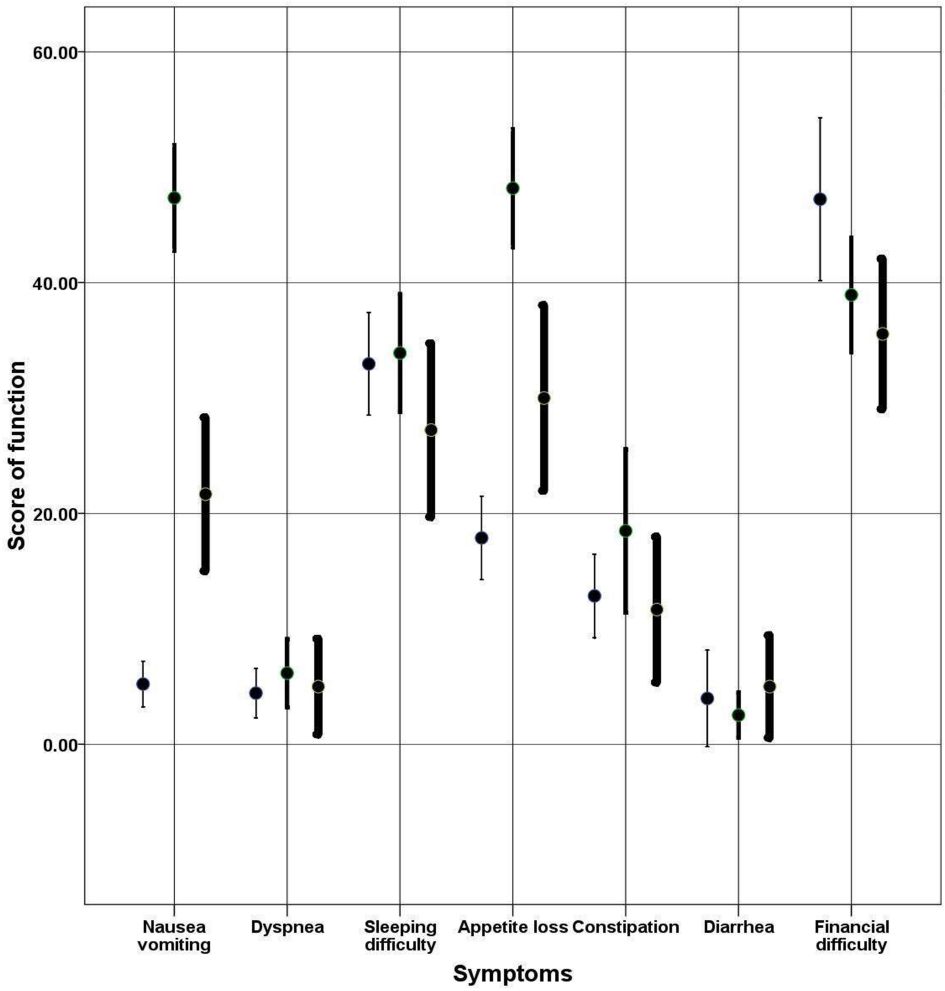

Figure 6.2 Patients' symptoms on the EORTC QLQ-C30 at baseline and post chemotherapy, for responders and non-responders.

Group:
Baseline
Post chemotherapy-no response
Post chemotherapy-response group

pain were also found using the SF-36 questionnaire. The dimensions score show that "no response" patients had lower QoL than "response" patients.

This study also found that both the response and no response groups showed the score deterioration in most of the dimensions and experienced worse symptoms compared to the baseline score (Table 6.3). Other factors which could have a negative impact on patients' QoL are patients' characteristics such as comorbidity, cancer diagnosis and stage of cancer. Meanwhile, only comorbidity showed significant impact on the physical function, pain and fatigue symptoms (data are not presented).

Table 6.3 Mean and standard deviation (SD) of QoL functions 5 days after chemotherapy, based on delayed emesis

	Response (Mean ± SD) *n* = 45	Non response (Mean ± SD) *n* = 134	*P* value
EORTC QLQ-C30			
General QoL	58.4 ± 17.5	58.4 ± 16.4	0.979
Physical function	71.6 ± 24.3	70.0 ± 22.1	0.673
Role function	66.6 ± 24.2	64.5 ± 24.8	0.590
Emotional function	93.9 ± 15.3	93.7 ± 13.2	0.956
Cognitive function	93.3 ± 16.3	92.7 ± 14.7	0.799
Social function	70.3 ± 19.9	72.1 ± 22.7	0.592
Pain	26.1 ± 24.6	31.9 ± 25.1	0.142
Fatigue	34.1 ± 22.2	41.3 ± 20.9	**0.032**
Nausea vomiting	21.7 ± 25.8	47.3 ± 25.2	**<0.001**
Dyspnea	5.0 ± 16.0	6.2 ± 16.2	0.650
Sleeping difficulty	27.2 ± 29.1	33.9 ± 28.2	0.140
Appetite loss	30.0 ± 31.1	48.2 ± 28.0	**<0.001**
Constipation	11.7 ± 24.4	18.5 ± 38.9	0.218
Diarrhea	5.0 ± 17.2	5.0 ± 34.6	0.993
Financial difficulty	35.6 ± 25.2	38.9 ± 27.2	0.423
SF-36			
General health perceptions	62.4 ± 20.5	59.1 ± 19.3	0.121
Physical function	57.6 ± 31.4	46.1 ± 32.4	**0.025**
Physical role function	23.8 ± 39.4	27.9 ± 39.6	0.504
Emotional role function	31.7 ± 45.3	25.5 ± 41.3	0.362
Mental health	77.4 ± 33.1	65.9 ± 30.9	**0.024**
Social function	63.3 ± 24.6	53.2 ± 21.3	**0.005**
Bodily pain	69.8 ± 27.4	60.8 ± 25.9	**0.034**
Fatigue	64.6 ± 19.1	61.3 ± 17.4	0.241
Health change	57.9 ± 33.1	51.1 ± 24.9	0.287

Values are means (SD). Significant score differences between the response and no-response groups are indicated in bold.

DISCUSSION

Our results show that, despite optimal initial prophylactic use of antiemetics followed by suboptimal prophylaxis for delayed nausea and emesis, most patients with gynecological cancer experience delayed emesis. We have to take into account that the standard of prophylactic antiemetic drugs which is used at our hospital is suboptimal. Despite this shortcoming we decided to study the relationship of CINV and QoL.

A previous study showed that around 70% of patients receiving chemotherapy in a community hospital experienced delayed emesis.[17] The present study shows a similar percentage of subjects experiencing delayed emesis (i.e., 74.9%). All patients were treated by a standard antiemetic regimen consisting of ondansetron and dexamethason one hour before the cisplatin treatment. Due to the cost of further ondansetron with dexamethason and certainly apepritant, suboptimal therapy with oral metoclopramide was prescribed for delayed emesis/vomiting. Based on the international guidelines, ondansetron or ganisetron in combination with dexamethasone on day 2 to day 5 should be given after highly emetogenic chemotherapy to prevent delayed emesis.[7] All of our patients were treated with metoclopramide over 5 days, after cisplatin treatment. Only 34.3% patients had complete response in the delayed phase. Poor control of patients' symptoms after chemotherapy interfered in our study with patients' QoL. In another study the metoclopramide efficacy was increased significantly by the augmentation of dexamethasone.[18]

The delayed emesis in our patient sample led to a significant negative impact on the patients' QoL. Significant impact was illustrated by more severe symptoms, such as fatigue, nausea, vomiting, appetite loss and pain after chemotherapy. Interestingly, the patients who did not experience delayed emesis also showed a deterioration of QoL. The scores of the various QoL-dimensions in EORTC QLQ-C30 questionnaire were lower than those in reference groups before the chemotherapy treatment. The symptom scores were also higher than those in the reference groups. This probably indicates that Indonesian gynecologic cancer patients have lower QoL and experience more severe symptoms than the same groups in the Netherlands before start of chemotherapy, possibly related to the suboptimal treatment of delayed nausea/emesis. A recent study in France suggested that the deterioration of physical function, role function and general health could be a reason for impaired QoL in newly diagnosed cancer patients.[19]

The present study showed that delayed emesis affects patients' symptoms such as fatigue, appetite loss and bodily pain. The higher score of the functions in the response group and the significant differences of function scores between the group of patients with 'response' and the 'no response' group indicate that delayed emesis interferes with patients' daily

function. Both 'response' and 'no response' groups showed that CINV interferes with patients' QoL. These findings are similar to other studies in cancer patients treated with moderately to highly emetogenic chemotherapy, despite the use of antiemetic. In addition, acute CINV affects patients' QoL even for the patients who do not experience nausea or vomiting during the delayed phase.[20] The patients' comorbidity should be considered as well as a factor which can impact on physical function, pain and fatigue.

In general, patients' QoL was decreased in our study after chemotherapy compared to baseline. These findings are similar to another study in community oncology setting across the US which revealed that chemotherapy-induced nausea and vomiting significantly interferes with patients' QoL.[1] Our study included cancer patients who received their first chemotherapy course with various emetogenic chemotherapy schedules.

General health perception, emotional and social function were maintained. This could be explained by the role of family and neighborhood support. One characteristic of the Indonesian society, especially in the rural area, is that many people come to the patient's house to give psychological support when the patient comes back from the hospital. This finding is supported by Noonan,[20] who reported that patients' QoL was not only affected by the symptoms of cancer and side effect of treatment, but also by the psychosocial condition, such as family support.The study on the survivorship in cancer patients suggested that the ability to return to family, social and work activities was an essential part of survivorship.[21]

Another study which used FLIE (Functional Living Index of Emesis) as the QoL instrument to study the relationship of CINV and patients' QoL, revealed that the score on FLIE after chemotherapy decreased significantly in the range of 21.6%-24.4%. Patients with CINV also had a decrease of health utility in the range of 15%-6.9%.[22] In addition, it has been reported that both acute and delayed emesis have significant impact on patients' daily functioning. Furthermore, it is frequently under-reported and untreated, since the patients experience these symptoms after they have left the hospital.[1] In our hospital a similar situation exists as patients leave hospital on average 4 hours after the chemotherapy has been given.

Different health care providers in the Western world have variously predicted the incidence rates of CINV and their prediction in prescription of antiemetics has also varied. For example, in patients receiving highly emetogenic chemotherapy, the use of 5-hydroxytriptamine receptor antagonists and dexamethasone as antiemetics led to an underestimation by the health providers in predicting delayed emesis.[23] In contrast, the use of aprepitant in combination with dexamethasone and 5-hydroxytriptamine receptor antagonists led to health care providers' overestimation in predicting delayed

CINV. Furthermore, it has been suggested that the health care providers increase their appreciation of delayed CINV incidence by using structured patients-reported outcome instruments.[5]

On the basis of the results in the present study, we also recommend that the health care providers in Indonesia should closely monitor delayed emesis and prescribe an appropriate antiemetic prophylaxis.

The results of our study indicate that poor control of delayed emesis in cancer patients treated by highly emetogenic chemotherapy unnecessarily reduces the patients' QoL. Thus, appropriately potent antiemetics should be used to prevent delayed emesis. In clinical practice, the oncologist who prescribes chemotherapy in combination with suboptimal chemotherapy, should be aware of delayed CINV, since the delayed emesis adversely affects patients after they have left the hospital. Furthermore, the delayed emesis should be closely monitored to improve the patients' QoL and patients' adherence in following the next cycles of chemotherapy. Cognitive-behavioural interventions, counseling and supportive therapy seem to be additional promising strategies to improve gynecological cancer patients' QoL and their survivorship.[1,21]

Conclusion

Patients with gynecological cancer in our study experienced severe symptoms, such as fatigue, nausea, vomiting, appetite loss and pain after chemotherapy despite adequate prophylactic use of antiemetics for acute nausea and vomiting but with insufficient prophylactic antiemetic therapy for chronic nausea and vomiting. These symptoms affected other domains as shown in both the EORTC QLQ-C30 and the SF-36 questionnaires.

Poor control of patients' chronic nausea and vomiting after chemotherapy has a negative impact on patients' QoL.

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7

General discussion and future perspectives

GENERAL DISCUSSION

Since chemotherapy-induced nausea and vomiting (CINV) is the most distressing side effect of chemotherapy,[1] the optimal use of antiemetic drugs for cancer patients has become a major goal for health professionals. Although international guidelines recommend the combination of a neurokinin-1 antagonist, a 5-hydroxytriptamine 3 receptor antagonist (5-HT3RA) and a corticosteroid as a standard antiemetic regimen for cancer patients treated with highly emetogenic cytotoxic agents,[2] these drugs are not at every Indonesian patient's disposal. First of all, the neurokinin-1 antagonist is not registered and thus not available in Indonesia and secondly, 5-HT3RAs are available at a high cost. For patients who are covered by the national health insurance the 5-HT3RAs are affordable, however, for the 40% of patients who are not covered by the national health insurance, these drugs are not affordable.

The suboptimal treatment with antiemetics results in symptoms of acute and delayed nausea and vomiting and could interfere with the patients' daily functions. In addition, patients may refuse to continue their cycles of chemotherapy because of CINV.[1] The suboptimal treatment of CINV in the acute phase can predict the presence of delayed CINV. Both acute and delayed CINV have a negative impact to the patients' quality of life (QoL),[3] but especially delayed CINV is known to be a strong predictor of the deterioration of patients' QoL.[1] Therefore, optimal prevention of CINV in the acute phase should be closely monitored not only for the acute effects but also to prevent the presence of delayed CINV.

The efficacy of antiemetic drugs in cancer patients is influenced by several factors, such as patients' age, gender, history of previous nausea vomiting and the use of alcohol.[2] Moreover, the role of genetic polymorphisms in 5-HT3RAs efficacy in Caucasian cancer patients has been evaluated.[3] Indeed, genetic polymorphisms in genes encoding enzymes and transporters involved in drug distribution and metabolism may affect the drugs' efficacy.

The 5-HT3RAs inhibit the impulse stimulation which will be transmitted into the chemoreceptor trigger zone and vomiting center, after passing through the distribution and biotransformation pathways. This stimulation is developed by the interaction of 5-HT3 receptors and 5-HT3 which is released by the cytotoxic drug.[4] The distribution of the 5-HT3RAs encompasses ABCB1 as a protein uptake transporter in the gastrointestinal and central nervous system and OCT1 as a protein uptake transporter in the hepatic cell.[7,8] In addition, CYP2D6 being one of the cytochrome P 450 subenzymes for oxidative metabolism plays a major role in the metabolism of the 5-HT3RAs.[5,9] Genetic polymorphisms in the genes encoding ABCB1,[10] OCT1,[5] CYP2D6[11] and 5-HT3RB, C and D[12-14] have indeed shown to modify the efficacy of the 5-HT3RAs in preventing the CINV in Caucasian

cancer patients. There is a strong biological rationale for such relationships. For example, the polymorphisms of the gene encoding CYP2D6 result in intermediate, poor or ultrarapid CYP2D6 metabolizer phenotypes and have therefore a significant influence on ondansetron and tropisetron's serum concentrations. Patients with lower ondansetron and tropisetron's serum concentrations experienced more severe nausea and vomiting compared to patients with higher ondansetron and tropisetron serum concentrations.[11]

In this new era of genetic polymorphisms influencing the antiemetics' efficacy, an emerging role of oncology pharmacists in ensuring the appropriateness of the prescription of antiemetics can be developed.[15] However, further studies are warranted to translate the results of pharmacogenetic studies in this field into the clinical oncology practice. Since there was only very limited information about antiemetics' efficacy and impact of the genetic polymorphisms on the antiemetics' efficacy in the Asian population, the studies described in this thesis were designed to answer those questions.

The general aims of this thesis are (1) to optimize the prevention and treatment of CINV by exploration of pharmacogenetic biomarkers , and (2) to determine the impact of CINV on QoL in Indonesian cancer patients. The association of pharmacogenetic biomarkers and antiemetics' efficacy is described in the first part of this thesis, subsequently the impact of CINV to the patients' QoL is discussed in the second part of the thesis.

Association of polymorphisms with antiemetics response in Indonesian cancer patients after being treated by highly emetogenic chemotherapy in community hospital-based setting

In **chapter 2**, we reviewed the literature on individualization of antiemetic drugs in oncology. It was confirmed that the pharmacogenetic studies of antiemetic in oncology were sparse. Interpatient variability of the 5-HT3RAs drug response is thought to be caused by genetic variation in proteins involved in the biotransformation and transport and pharmacodynamics of the drugs. The 5-HT3RAs are substrates of ABCB1 and are metabolized by the CYP2D6 isoenzyme.[10,16] Indeed, some studies in Caucasian cancer patients show that variability of the antiemetic response of ondansetron and tropisetron are related to the C3435T variant of the *ABCB1* gene and to the phenotypes of *CYP2D6*.[10,16] Furthermore, the *5-HT3B* and *C* receptor gene variabilities were found to be predictor of ondansetron's efficacy as well. The 100_102AAG deletion variant of the *5-HT3B* receptor gene and the K163N variant of the *5-HT3C* receptor gene were shown to be related to response upon ondansetron treatment in Caucasian cancer patients.[12,16,17] However, further studies are warranted to replicate and confirm these pharmacogenetic associations regarding the 5-HT3RAs.

One cannot simply translate the findings of pharmacogenetic studies in one ethnic group to another. One reason is that allele frequencies of genetic variations may greatly vary among ethnicities. Therefore, the findings of the studies described in chapter 2, which were performed in Caucasian cancer patients, may not by definition hold true for Indonesian cancer patients. To explore the potential of these findings in Indonesian cancer patients we started with comparing allele frequencies of variants in the *5-HT3B* receptor gene between Caucasians and Indonesians.

The haplotypes frequencies of the gene encoding 5-HT3B receptor in Indonesian cancer patients and Caucasian healthy subjects are compared in **chapter 4**. The frequencies of AAGAG and AAGGG haplotypesin the gene encoding 5-HT3B receptor between Indonesians and Caucasians differ significantly (OR = 1.50; 95% CI: 1.18-1.90 and OR = 0.58; 95% CI: 0.58-0.79, respectively). The frequency of AAGAG haplotype in Indonesians is higher than those in Caucasians, however, the frequency of AAGGG haplotype in Indonesians is lower than those in Caucasians. This finding can be used to understand interethnic variation of disease and drug response related to the 5-HT3B receptor. However, in pharmacogenetic studies regarding the *5-HT3B* receptor gene, the deletion AAG variant is the most studied for association with drug response. The subjects with deletion AAG variant experience more severe nausea and or vomiting induced by chemotherapy or drugs.[17,18]

In our study, the frequency of the deletion AAG, and the haplotype including the deletion, was not significantly different between Indonesians and Caucasians. However, there were significant differences between the Indonesian and Caucasian population in the distribution of the pairs of haplotypes including the deletion AAG. Thus, differences in 5-HT3RA antagonist response between Asians and Caucasians may be attributable to the differences in haplotype pairs that exist in each population. Further studies are needed to understand the effect of the deletion AAG or its haplotype in Asian patients in relation to unresponsiveness to 5-HT3RAs.

In **chapter 3**, we conducted a prospective cohort study which enrolled 202 chemotherapy naïve patients. Patients were treated with cisplatin at a dosage ≥ 50 mg/m^2 as monotherapy or as combined chemotherapy. Ondansetron 8 mg and dexamethasone 8 mg intravenously were standard antiemetic therapy for prevention of acute CINV. Meanwhile, metoclopramide 10 mg orally, 3 times per day as fixed prescription was given until 5 days after chemotherapy to prevent delayed CINV. The following SNPs were determined in *ABCB1*: rs1045642, rs2032582, rs1128503; in *5-HT3B-R*: rs3831455, rs4938058, rs7943062 and in *CYP2D6*: rs16947 (*CYP2D6*2*), rs3892097 (*CYP2D6*4*), rs1065852 (*CYP2D6*10*) using Taqman assays to understand the association between gene polymorphism and antiemetic

drugs response. It was confirmed that ondansetron and dexamethasone could prevent about 80% of patients from acute nausea and 70% of 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 the use of the neurokinin-1 antagonist aprepitant during the acute phase or with the use of dexamethasone for prevention during the delayed phase. Earlier studies suggested that the antiemetic response is related to patients' characteristics, such as younger age, female, history of alcohol drinking and history of emesis during pregnancy.[19] However, in our study such a relationship could not be confirmed probably due to small sample size of male patients and no patients have history of alcohol drinking.

Regarding pharmacogenetic associations, this study showed that genetic variants in *ABCB1*, *5-HT3B receptor* and *CYP2D6* were not related to ondansetron efficacy in acute CINV. However, the carriership of the CTG haplotype in the *ABCB1* gene increases the risk of delayed CINV and therefore modifies the effect of metoclopramide. The proposed mechanism is that passage of metoclopramide across the blood-brain barrier is increased in 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-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.[7]

According to the haplotypes of *5-HT3B* receptor gene, we found that the percentage of patients who experienced acute nausea and vomiting seemed to be higher in carriers of the AAGAG haplotype, although it did not reach statistical significance. Patients carrying the deletion AAG haplotype in 5-HT3B receptor experienced a non statistical significant of lower grade nausea and a higher grade vomiting in the acute phase compared to the other haplotypes. Since the low frequency of predicted phenotypes of UM and PM in Asian,[6] we only found predicted phenotypes of EM and IM in our patients. Thus, the role of CYP2D6 phenotype in explaining variability in ondansetron and metoclopramide efficacy in Asians seems to be limited if present at all.

The impact of delayed CINV on patients QoL

QoL is one of the cancer patients' outcome during their treatment. However, QoL studies in Indonesia are still rare. One reason is that validated instruments to assess QoL in the Indonesian language are absent. Therefore, we developed an Indonesian version of a QoL questionnaire to assess psychometric properties in cancer patients (**chapter 5**). A

forward-backward translation of the EORTC QLQ-C30 into the Indonesian language was accomplished and in compliance with the procedures developed by the EORTC Quality of Life Study Group.[7] The validity evaluation included convergent, discriminant, known-groups validity, construct validity and factor analysis. The Indonesian version of SF-36 was used as a gold standard in the construct validity evaluation. After the pilot testing, validity and reliability evaluation, the Indonesian version of EORTC QLQ-C30 was concluded to be acceptable for assessing psychometric properties and could be used to measure Indonesian cancer patients' QoL. This scale development will help clinicians to describe the human side of cancer treatment in Indonesia. The practicing oncologist can benefit greatly from the work that was performed in developing and validating this scale, by applying the instrument to the selection of treatment modalities based on both treatment efficacy and the patient's wishes. In the future, the development of the instruments in an Indonesian version is required to achieve ideal tools to measure psychometric properties. We applied the instrument developed in chapter 6 to assess the QoL in Indonesian cancer patients treated with highly emetogenic chemotherapy. The hypothesis was that the occurrence of delayed CINV in Indonesian cancer patients would lead to significant negative impact on patients' QoL.

In **chapter 6** it is confirmed that the use of suboptimal prophylactic antiemetics during the delayed phase of CINV decreases patients' QoL. This study was carried out as a prospective non-interventional cohort design, thus all of the gynecologic cancer patients treated with antiemetic drugs who were appropriate to the hospital standard were included in the QoL study. Ondansetron and dexamethasone were administered to the patients one hour before cisplatin treatment. After that, metoclopramide was given to the patients during 4 days. Despite prophylaxis there were significant differences between the response and no response groups in fatigue, nausea, vomiting, and appetite loss. The "no response" patients experienced more severe symptoms than "response" patients in whom the attempted prevention of nausea and vomiting was effective, according to the diary data. We also considered patients' characteristic which could interfere with patients' QoL after chemotherapy, but we did not find the significant influence of the characteristics. We conclude that delayed emesis should be closely monitored which could improve the patients' QoL in addition to the patients' adherence in the next cycles of chemotherapy. Cognitive-behavioral interventions, counseling and supportive therapy seem to be additional promising strategies to improve gynecological cancer patients' QoL and their survivorship.[22,23]

Perspectives

Improvement of control of both acute and delayed CINV in cancer patients in Indonesia is needed to get maximal benefit from chemotherapy. Therefore, the optimal antiemetic drugs to prevent delayed CINV should be recommended and applied according to the international standard. However, some financial difficulties related to the cost of antiemetics should be considered by the physician in Indonesia with prescribing another antiemetic. The physician may prescribe other antiemetics which have similar efficacy as the internationally recommended antiemetic regimen or increase the dose of standard antiemetics.

According to this situation, besides ondansetron, the other 5-HT3RAs can be used in combination with dexamethasone to reach optimal antiemetic treatment. The different pharmacokinetic profiles of the other 5-HT3RAs such as tropisetron, palonosetron, dolasetron and granisetron can modify the antiemetic response. Palonosetron which has the longest elimination half-life among the 5-HTRAs can be considered in preventing delayed nausea vomiting.[24] Alternatively, other antiemetics to prevent the delayed emesis could be considered, besides metoclopramide. Gabapentin and olanzapine may be alternative antiemetics to prevent acute and delayed CINV in Indonesia health perspective. These two drugs are available in Indonesia at affordable costs.[25,26]

The benefits of chemotherapy in cancer care are usually depicted in terms of response rate, progression free survival, overall survival, and remission rate. Increasingly, QoL from the patient's perspective is considered as a clinical endpoint of treatment. Valid instruments in different languages are needed to assess the cancer patients' daily function across the world, both in developed and developing countries. An Indonesian version of EORTC QLQ-C30 is now available and this questionnaire is suitable for all types of cancer. For the future, development of cancer type specific questionnaires such as for cervical cancer in Indonesian language is warranted.

As shown delayed CINV has significant impact on the patients' QoL. Therefore, supportive care by healthcare providers before, during and after chemotherapy should be improved and benefit the patient. This supportive treatment needs broad collaboration among the oncologist, psychologist, nurse, pharmacist and the patient's family. Specifically for Indonesia, the close social relationship between the cancer patient, family and neighborhood in Indonesia offers an opportunity to increase some of the patients' functions, despite the limited health facilities.

Since we found no significant associations between patients' characteristics or genetic polymorphisms and antiemetic response, the reason of the high number of non-responders

in acute and delayed CINV (> 20%) is still unclear. Only involvement of the carriership of CTG in the *ABCB1* gene could explain suboptimal effects of antiemetic response to metoclopramide in the delayed phase. Functional studies, for example pharmacokinetics of metoclopramide, to confirm this relationship need to be performed.

Interestingly, there are major differences in interethnic response to drugs. Differences in genetic variations among races may explain the variability of antiemetics' response in oncology.[8] To some extent interethnic differences in drug response can be predicted form differences in allele frequencies among races. For example, for CYP2D6 phenotype it is known that the frequency of PMs in Asians is 2.0-4.8%, while in Caucasian it is 5.0-10.0%.[27] Therefore, it can be predicted that the impact of CYP2D6 genetic variants on drug response of CYP2D6 substrates is lower in Asians as compared to in Caucasians. Indeed, we did not find an association between CYP2D6 phenotypes and ondansetron and metoclopramide efficacy. An alternative explanation is that ondansetron is also metabolized by CYP3A4 and polymorphisms in the genes encoding CYP3A4/5 may have a role in the pharmacokinetic of ondansetron.

In addition, drugs like ondansetron have a complex pharmacology and therefore studies on the variation in the genes encoding 5-HT3B receptor may not fully account for variability in the pharmacodynamics. Since ondansetron also binds to the 5-HT1A, C, D, α-adrenergic, and μ-opioid receptors, future pharmacogenetic studies should also include genetic variants in these receptors.

In this thesis, we presented that the unsatisfactory antiemetic drugs effect in acute and delayed phase may cause the deterioration of QoL. In order to explore the causal factors of the unsatisfactory drug response, pharmacogenetics related to genes encoding enzymes and transporters which have significant role on disposition and metabolism of ondansetron and metoclopramide was investigated. Further studies would include pharmacokinetics of ondansetron and metoclopramide.

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8

Summary

Cancer is the fourth leading cause of death in Indonesia in 2005 and it is estimated to become the third in 2030. Chemotherapy, one of the cancer treatment choices, can increase the progression-free survival and overall survival time. However, patients who are treated with cytotoxic agents are also experiencing side effects and they may refuse to continue the next cycles of chemotherapy.

Nausea and vomiting are well known side effects related to chemotherapy. Indeed, nausea and vomiting are the most distressing side effects of chemotherapy in cancer patients. Dopamine, serotonin and neurokinin1 are thought to be the neurotransmitters that play role in the pathophysiology of Chemotherapy Induced Nausea Vomiting (CINV). Thus, the antagonists of those neurotransmitters are considered as prophylactic antiemetics for CINV. In the 1990s, the use of 5-hydroxytriptamine 3 receptor antagonists (5-HT3RAs) highly improved the patients' response rate to antiemetic drugs. In addition, the combination of a neurokinin 1 antagonist, a 5HT3RA and a corticosteroid can further increase the response rate up by 15% in acute phase and 20% in delayed phase. Thus, the international guideline of clinical oncology recommend this combination as prophylactic antiemetic drugs in the acute phase and a combination of dexamethasone – metoclopramide as prophylactic antiemetics in the delayed phase.

However, when the standard antiemetic drug regimens are administered to patients, there are still 20-30% patients in the acute phase and 40% patients in the delayed phase experiencing CINV. Thus, there is a high interindividual variability in response to antiemetic drugs in oncology patients. Some patient characteristics such as female gender, younger patients and history of alcohol drinking could increase the risk of CINV from 20% to 70%. Therefore, individualizing of the use of antiemetics could start by considering the patient characteristics. This thesis focuses on optimizing the prevention and treatment of CINV by exploration of pharmacogenetic biomarkers and determining the impact of CINV on QoL in Indonesian cancer patients.

The fundamentals and clinical pharmacology including the pharmacogenetics of antiemetic drugs applied in oncology are described in **chapter 2**. This chapter clarifies the mechanisms of action of antiemetic drugs in preventing acute and delayed CINV based on the neurotransmitters which play a role in CINV. The pharmacogenetic studies on 5-HT3RAs related to the *ABCB1* gene, *5-HT3 receptors* genes and *CYP2D6* in Caucasian cancer patients are presented.

Pharmacogenetic study of ondansetron and metoclopramide

In **chapter 4**, we found that Indonesian cancer patients had significantly different AAGAG and AAGGG haplotype frequencies of the gene encoding the 5-HT3B receptor compared to healthy Caucasians. Moreover, there were significant differences between the Indonesian and Caucasian population in the distribution of the pairs of haplotypes including the deletion AAG. Therefore, the possible differences in 5-HT3RAs response between Asians and Caucasians may not be ascribed to differences in the frequency of the deletion AAG but may be due to the differences in haplotype pairs that exist in the populations. This finding could be useful for understanding interethnic differences in drug response of drugs targeting the 5-HT3B receptor in cancer treatment related emesis.

A clinical pharmacogenetic study investigating the association of variants in the genes encoding ABCB1, the 5-HT3B receptor and CYP2D6 with CINV in Indonesian cancer patients is presented in **chapter 3**. This study shows that there is no association of variants between genes encoding ABCB1, the 5-HT3B receptor or CYP2D6 and ondansetron response. However, the carriership of the CTG haplotype in the *ABCB1* gene increases the risk of delayed CINV and may therefore modify the effect of metoclopramide in the delayed phase. The proposed mechanism is that passage of metoclopramide across the blood-brain barrier is increased in 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-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.

Impact of CINV to the patients' quality of life

Chapter 5 of this thesis provides the results of a study on the translation and validation of the EORTC QLQ-C30 in the Indonesian language. The forward-backward translation of EORTC QLQ-C30 into the Indonesian language was in compliance with the procedures developed by the EORTC Quality of Life Study Group. The validity evaluation included convergent, discriminant, known-groups validity, construct validity and factor analysis. The Indonesian version of SF-36 was used as gold standard in the construct validity evaluation. After the pilot testing, validity and reliability evaluation, the Indonesian version of EORTC QLQ-C30 was suggested to have acceptable psychometric properties and could be used to measure Indonesian cancer patients' quality of life.

Chapter 6 reports that the use of suboptimal prophylactic antiemetics during the delayed phase of CINV decreases patients' quality of life. The augmentation of dexamethasone during the delayed phase could increase the metoclopramide efficacy. This study was carried out by prospective non-interventional cohort design, thus all of the gynecologic cancer patients were treated by antiemetic drugs which were according to the hospital standard. The ondansetron and dexamethason were administered to the patients one hour before cisplatin treatment. After that, metoclopramide was given to the patients over 4 days.

The **final chapter** of this thesis is the discussion of the result and the future directions.

Further study is needed to investigate the association between pharmacokinetic profiles of metoclopramide and its efficacy during the delayed phase to confirm the modification effect of metoclopramide due to the carriership of CTG haplotypes of *ABCB1* gene. The pharmacogenetic studies of ondansetron can be expanded in the future by including variants encoding other relevant genes such as the *CYP3A4*, *5-HT1B*, *5-HT1C*, *α-adrenergic*, *μ-opioid*, *5-HT3A*, *B*, *C*, *D* and *E*.

Meanwhile, using combination of the other 5-HT3RAs besides ondansetron, and dexamethasone to get the optimal treatment of antiemetic during the acute phase should be considered. Otherwise, the augmentation of dexamethasone during the delayed phase may increase the metoclopramid efficacy. Gabapentin and olanzapine may be the alternatives of antiemetics to prevent acute and delayed CINV in Indonesia health perspective.

In the future, the incidence of cervical cancer will increase in Indonesia, and therefore further studies aimed at translation and validation of EORTC QLQ for specific types of cancer such as cervical cancer is called.

The high impact of CINV on patients' quality of life warrants adequate supportive care from the healthcare providers before, during and after chemotherapy is applied. This supportive treatment needs close collaboration between the oncologist, psychologist, nurse, pharmacist and the family. The close social relationship among the cancer patient, the family and neighborhood in Indonesia could increase some of the patients' functions, despite the limited health facilities.

9

Rangkuman

(Summary in Indonesian)

Kanker merupakan penyebab kematian peringkat keempat di Indonesia pada tahun 2005 dan diperkirakan akan menjadi penyebab kematian peringkat ketiga pada tahun 2030. Kemoterapi masih merupakan salah satu pilihan terapi untuk kanker dan dapat meningkatkan *progression-free survival* (PFS) dan *overall survival time* (OS) pasien kanker. Namun pasien yang mendapat terapi dengan bahan sitotoksik tersebut juga akan mengalami efek samping obat. Akibat mengalami efek samping obat, pasien mungkin akan menolak untuk melanjutkan kemoterapi siklus selanjutnya.

Mual dan muntah merupakan salah satu efek samping kemoterapi yang paling dikenal dan paling dicemaskan oleh pasien. Dopamin, serotonin (hidroksitriptamin) dan neurokinin-1 merupakan neurotransmiter yang berperan dalam patofisiologi mual muntah pada pemberian kemoterapi. Oleh karena itu obat yang bekerja sebagai penghambat reseptor dopamine, serotonin dan neurokinin-1 merupakan antiemetik profilaksi mual muntah pada pemberian kemoterapi. Sejak 1990, antagonis reseptor 5-hidroksitriptamin 3 (5-HT3) digunakan untuk meningkatkan respon pasien terhadap terapi antiemetik konvensional. Kombinasi antagonis neurokinin-1, antagonis reseptor 5-HT3 dan deksametason menunjukkan peningkatan respon pasien sebesar 15% pada fase akut dan 20% pada fase tertunda. Oleh karena itu Perhimpunan Ahli Onkologi Klinis Internasional merekomendasikan kombinasi pengobatan tersebut pada fase akut dan kombinasi metoklopramid -deksametason pada fase tertunda.

Meskipun pasien kanker sudah mendapat terapi antiemetik profilaksi yang sesuai dengan standar, namun 20-30% penderita pada fase akut dan 40% pasien pada fase tertunda masih mengalami mual muntah akibat kemoterapi. Efek yang tidak optimal ini dapat disebabkan karena variasi individu. Faktor karakteristik pasien seperti wanita, usia muda dan riwayat konsumsi alkohol meningkatkan risiko terjadinya mual muntah akibat pemberian kemoterapi dari 20% menjadi 70%. Sehingga pemberian antiemetik pada fase akut dan tertunda sebaiknya mempertimbangkan variasi individu dan karakteristik pasien.

Tujuan penyusunan tesis ini adalah untuk optimalisasi terapi dan pencegahan mual muntah pada pemberian kemoterapi dengan mempertimbangkan aspek farmakogenetik dari biomarker dan mengetahui pengaruh mual muntah pada pemberian kemoterapi terhadap kualitas hidup pasien kanker.

Bab II dari tesis ini berisi tentang *review* farmakologi fundamental, klinik, dan genetik dari antiemetik dibidang onkologi. Di dalam bab ini dijelaskan mekanisme aksi dari obat-obat antiemetik dalam mengatasi mual muntah akibat kemoterapi baik pada fase akut maupun fase tertunda. Adanya hubungan antara variasi gen *ABCB1* (*ATP-Binding Casette Sub-family B member 1*), *5-HT3R* dan *CYP2D6* pada pasien kanker ras Kaukasia juga dijelaskan dalam bab ini.

Penelitian farmakogenetik ondansetron dan metoklopramid

Di dalam **Bab IV**, ditemukan adanya perbedaan frekuensi haplotipe AAGAA dan AAGGG yang signifikan pada ras Asia dan Kaukasia. Selanjutnya, ditemukan juga adanya perbedaan distribusi pasangan haplotipe deletion AAG antara kedua ras tersebut. Hal ini memungkinkan timbulnya perbedaan respon antiemetik antara ras Asia dan Kaukasia. Penelitian ini juga menjelaskan adanya perbedaan respon berdasarkan aspek farmakodimanika reseptor 5-HT3B pada kedua ras tersebut.

Hubungan antara variasi gen yang mengkoding ABCB1, reseptor 5-HT3B dan CYP2D6 dengan mual muntah akibat kemoterapi pada pasien kanker di Indonesia dijelaskan di **Bab III**. Hasil penelitian ini menemukan bahwa tidak ada hubungan antara variasi gen yang mengkoding ABCB1, reseptor 5-HT3B dan CYP2D6 dan respon ondansetron. Namun, pembawa haplotipe CTG dari gen *ABCB1* dapat meningkatkan risiko mual muntah akibat kemoterapi pada fase tertunda dan akan memodifikasi efek dari metoklopramid pada fase tersebut. Metoklopramid dapat melalui sawar otak dengan adanya inaktivasi P-glikoprotein (P-gp). Sedangkan tempat aksi metoklopramid adalah di ventrikel keempat yang terletak di luar sawar otak. Dengan adanya P-gp yang inaktif maka lebih banyak metoklopramid yang mampu melalui sawar otak sehingga menimbulkan efek samping sindroma ekstrapiramidal. Namun hanya sedikit metoklopramid yang tersedia di ventrikel ke empat, sehingga efikasi metoklopramid berkurang.

Pengaruh mual muntah akibat kemoterapi terhadap kualitas hidup pasien

Bab V tesis ini menjelaskan tentang proses translasi dan validasi kuesioner EORTC QLQ-C30 ke dalam versi bahasa Indonesia. Proses translasi *forward-backward* kuesioner ini ke dalam bahasa Indonesia mengikuti prosedur yang sudah ditentukan oleh *EORTC Quality of Life Study Group*. Prosedur validasi meliputi validasi konvergen, validasi diskriminan, validasi kelompok, analisis faktor dan validasi konstrak. Kuesioner SF-36 versi Indonesia digunakan sebagai acuan dalam validasi konstrak. Setelah dilakukan uji pendahuluan dan uji validitas, maka kuesioner EORTC QLQ-30 dapat digunakan sebagai instrument pengukur kualitas hidup pada pasien kanker di Indonesia.

Bab VI menjelaskan kualitas hidup pasien setelah pemberian kemoterapi. Pada studi ini ditemukan adanya pemberian antiemetik suboptimal pada fase tertunda yang menimbulkan mual muntah pada pemberian kemoterapi sehingga mengurangi kualitas hidup pasien. Untuk itu disarankan penambahan deksametason pada fase ini untuk meningkatkan efikasi metoklopramid. Rancangan penelitian ini adalah kohort prospektif non intervensional, sehingga jenis dan regimen antiemetik yang diberikan kepada pasien selama fase akut dan

tertunda sesuai dengan standar yang sudah ditentukan di rumah sakit. Antiemetik yang diberikan pada pasien adalah ondansetron 8 mg iv dan deksametason 8 mg iv satu jam sebelum terapi cisplatin dan metoklopramid 10 mg oral pada hari kedua sampai kelima setelah kemotgerapi.

Dalam **bab terakhir** tesis ini, peneliti berharap adanya penelitian lanjutan untuk mengetahui hubungan profil farmakokinetik dari metoklopramid dan efikasinya pada fase tertunda. Hal ini ditujukan untuk mengkonfirmasi efek modifikasi haplotipe CTG pada gen *ABCB1* terhadap metoklopramid. Selanjutnya studi farmakogenetik ondansetron dapat dilakukan pada gen yang mengkode *CYP3A4*, *5-HT1B*, *5-HT1C*, *α-adrenergic*, *μ-opioid*, *5-HT3A*, *B*, *C*, *D* dan *E*.

Pemberian antiemetik golongan antagonis reseptor 5-HT3 pada fase akut, selain kombinasi ondansetron-deksametason perlu dipertimbangkan juga jenis yang lain. Penambahan gabapentin atau olanzapine pada kombinasi ondansteron-deksametason dapat digunakan sebagai alternatif antiemetik pada fase akut dan tertunda di Indonesia.

Insidensi penyakit kanker di Indonesia semakin meningkat. Sehingga studi lebih lanjut mengenai translasi dan validasi EORTC QLQ-C30 yang sesuai dengan tipe kanker yang spesifik sangat diperlukan di Indonesia.

Adanya penurunan kualitas hidup yang cukup signifikan akibat efek mual muntah pada pemberian kemoterapi menunjukkan pentingnya peningkatan pelayanan penunjang di penyedia sarana kesehatan baik sebelum, selama atau sesudah kemoterapi di Indonesia. Pelayanan penunjang ini memerlukan kerjasama dari ahli onkologi, ahli psikologi, perawat, apoteker dan juga dari keluarga pasien sendiri. Adanya hubungan sosial yang sangat dekat antara pasien, keluarga pasien dan lingkungan sosial dapat meningkatkan kualitas hidup pasien setelah kemoterapi meskipun fasilitas pelayanan kesehatan yang ada cukup terbatas.

10

Samenvatting

(Summary in Dutch)

Kanker was de vierde doodsoorzaak in Indonesië in 2005 en naar verwachting wordt kanker de derde doodsoorzaak in 2030. Chemotherapie, één van de behandelingsmogelijkheden van kanker, kan de progressie-vrije overleving en de algehele duur van overleving vergroten. Echter, de patiënten die worden behandeld met chemotherapie ondervinden veel bijwerkingen die kunnen resulteren in het staken van de therapie.

Misselijkheid en braken zijn bekende bijwerkingen van chemotherapie en worden als zeer belastende bijwerkingen ervaren door patiënten met kanker. Verondersteld wordt dat de neurotransmitters dopamine, serotonine en neurokinine 1 een cruciale rol spelen bij het ontstaan van door chemotherapie geïnduceerde misselijkheid en braken (Chemotherapy Induced Nausea and Vomiting, hierna: CINV).

Antagonisten van deze neurotransmitters worden met succes toegepast als profylactische anti-emetica voor CINV. In de jaren negentig werd de behandeling van CINV met de introductie van 5-hydroxytriptamine receptor antagonisten (5-HT3RAs) sterk verbeterd. Door combinatie van een 5HT3RA en een corticosteroïd werd de responskans verder verhoogd met 15% in de acute fase en 20% in de late fase. Daarom adviseert de internationale richtlijn voor klinische oncologie deze combinatie als profylactische anti-emetische geneesmiddelen in de acute fase en een combinatie van dexamethason en metoclopramide als profylactisch beleid in de late fase.

Echter, als dit standaard anti-emetisch regime wordt toegepast bij patiënten, blijkt nog steeds 20 tot 30% van de patiënten in de acute fase en 40% in de late fase last van CNIV te ondervinden. Dit betekent dat er onder de behandelde patiënten met kanker een grote interindividuele variabiliteit in respons op anti-emetica bestaat. Sommige patiëntkarakteristieken, zoals het vrouwelijke geslacht, jonge leeftijd en alcoholgebruik, kunnen de kans op CINV verhogen van 20 naar 70%. Dit geeft aan dat patiëntkarakteristieken een rol kunnen spelen bij het individueel afstemmen van de anti-emetische therapie. Dit proefschrift richt zich op het bepalen van de gevolgen van CINV op de kwaliteit van leven (hierna: QoL) in Indonesische patiënten met kanker en op het verder optimaliseren van de behandeling en voorkomen van CINV door toepassing van farmacogenetische biomarkers.

De basisprincipes en klinische farmacologie inclusief de farmacogenetica van de anti-emetica gebruikt in de oncologie worden beschreven in **hoofdstuk 2**. Dit hoofdstuk beschrijft de werkingsmechanismen van de anti-emetica bij het voorkomen van acute en vertraagde CINV in relatie tot de neurotransmitters die een rol spelen bij CINV. De farmacogenetische onderzoeken naar 5HT3RA's in relatie tot *ABCB1*, *5-HT3 receptoren* en *CYP2D6* in Kaukasische patiënten met kanker worden gepresenteerd.

Farmacogenetisch onderzoek van ondansetron en metoclopramide

In **hoofdstuk 4** laten wij zien dat Indonesische patiënten met kanker significant andere frequenties hebben van het AAGAG en AAGGG haplotype van het gen dat codeert voor de 5-HT3B receptor in vergelijking met gezonde Kaukasiërs. Bovendien waren er significante verschillen tussen de Indonesische en Kaukasische populatie in de verdeling van de haplotypen, waaronder de depletie van AAG. Daarom kan het mogelijke verschil in respons in 5-HT3RA tussen Aziaten en Kaukasiërs niet worden toegeschreven aan de verschillen van de AAG-depletie, maar wellicht wel aan het verschil in haplotypen tussen beide etniciteiten. Deze belangrijke bevinding kan de interetnische verschillen in respons van op 5-HT3B receptor antagonisten bij patiënten met kanker mogelijk verklaren.

Een klinisch farmacogenetisch onderzoek naar de associatie tussen variaties in de genen die coderen voor ABCB1, de 5-HT3B receptoren en CYP2D6 en CINV in Indonesische patiënten met kanker wordt gepresenteerd in **hoofdstuk 3**. Dit onderzoek laat zien dat er geen associatie is tussen de variaties in deze genen en de respons op ondansetron. Echter, dragerschap van het CTG haplotype in het *ABCB1* gen, dat codeert voor het transportereiwit P-gp, verhoogt de kans op vertraagd CINV en zou daarmee het effect van metoclopramide in deze fase kunnen beïnvloeden. Het veronderstelde werkingsmechanisme is dat passage van metoclopramide over de bloed-hersenbarrière is toegenomen bij afwezigheid van actief P-gp. Immers, de plaats van werking van metoclopramide is gelegen in de vierde ventrikel, die zich achter de bloed-hersenbarrière bevindt. De rol van P-gp in het transport van metoclopramide naar het centrale zenuwstelsel stemt ook overeen met het gegeven dat er een verhoogde metoclopramideconcentratie in het centrale zenuwstelsel wordt gevonden in patiënten met een inactief P-gp dat leidt tot extrapyramidale bijwerkingen.

De invloed van CINV op de kwaliteit van leven

In **hoofdstuk 5** van dit proefschrift worden de resultaten getoond van het onderzoek naar de vertaling en validatie van de EORTC QLQ-C30 in de Indonesische taal. De "forward-backward" vertaling van de EORTC QLQ-C30 in de Indonesische taal voldeed aan de procedures zoals ontwikkeld door de EORTC Quality of Life Study Group. De evaluatie van de validiteit betrof vooral constructvaliditeit. De Indonesische versie van de SF-36 is als gouden standaard gebruikt in het onderzoek van de psychometrische kenmerken van het vertaalde instrument. In het pilotonderzoek, en bij de validatie- en betrouwbaarheidsevaluatie, liet de Indonesische versie van de EORTC QLQ-30

acceptabele psychometrische eigenschappen zien en werd geconcludeerd dat deze geschikt is om de kwaliteit van leven van Indonesische patiënten met kanker vast te stellen.

Hoofdstuk 6 laat zien dat het gebruik van een suboptimaal profylactische anti-emeticum regime tijdens de vertraagde fase van CINV de kwaliteit van leven van de patiënt negatief beïnvloedt. Door toevoeging van dexamethason tijdens de vertraagde fase zou de metoclopramide effectiviteit kunnen verbeteren. Dit onderzoek werd uitgevoerd als een prospectief niet interveniërend cohortonderzoek, waarbij alle patiënten met gynaecologische kanker volgens de vigerende lokale ziekenhuisstandaard met anti-emetica werden behandeld. Ondansetron en dexamethason werden één uur voor de toediening van cisplatine aan deze patiënten toegediend. Daarna werd metoclopramide gegeven gedurende vier dagen.

In dit **laatste hoofdstuk** worden de resultaten van dit proefschrift bediscussieerd en worden toekomstige onderzoeken voorgesteld.

In de toekomst is aanvullend onderzoek nodig om de de associatie tussen de farmacokinetiek van metoclopramide en de effectiviteit van dit middel tijdens de vertraagde fase van CINV te bestuderen en om de gevonden relatie met het dragerschap van het CTG-haplotype van het *ANCB1* gen te kunnen verklaren. Het farmacogenetisch onderzoek met ondansetron zou in de toekomst uitgebreid kunnen worden met andere potentieel relevante genen zoals *CYP3A4*, *5-HT1B*, *5-HT1C*, *α-adrenerge*, *μ-opioide*, *5-HT3A*, *B*, *C*, *D* en *E*.

Toepassing van de combinatie van andere 5-HT3RA's dan ondansetron, met dexamethason, met als doel om een optimale anti-emetische behandeling gedurende de acute fase te bereiken, zou kunnen worden overwogen. Ook zou de toevoeging van dexamethason tijdens de vertraagde fase de effectiviteit van metoclopramide kunnen verhogen. Gabapentine en olanzapine zouden alternatieve anti-emetica kunnen zijn bij de profylaxe van acuut en vertraagd CINV vanuit het perspectief van de Indonesische gezondheidszorg.

In de toekomst zal de incidentie van baarmoederhalskanker in Indonesië toenemen en om die reden zouden meer onderzoeken gedaan moeten worden naar de vertaling en validatie van ziektespecifieke versies van de EORTC QLQ C30, zoals baarmoederhalskanker.

De grote gevolgen die CINV heeft op de kwaliteit van leven van de patiënt vereisen een adequate ondersteunende therapie vóór, tijdens en na de behandeling met chemotherapie. Deze ondersteunende behandeling vereist een nauwe samenwerking tussen oncoloog, psycholoog, verpleegkundige, apotheker en familie.

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About the author

CURRICULUM VITAE

Dyah Aryani Perwitasari was born on 30 April 1976, in Semarang, Indonesia. Now, she lives with her husband and two children in Yogyakarta, Indonesia. She got her bachelor degree in 1998 and Pharmacist degree in 1999 from the Pharmacy Faculty of Gadjah Mada University, Yogyakarta. She finished her master degree from 2001 to 2003 as Magister of Clinical Pharmacy at the Gadjah Mada University. In 2006, she decided to continue her degree in Medicine at the Faculty of Medicine, Gadjah Mada University. She graduated cum laude on 14th October 2011.

The opportunity to take her PhD degree in Leiden University Medical Center (LUMC), Leiden, The Netherlands, with Prof. Dr. H.-J. Guchelaar (Head Department of Clinical Pharmacy and Toxicology) and Prof. Dr. J.W.R. Nortier (Head Department of Clinical Oncology) as the promotors was kindly supported by the Netherlands Organization for International Cooperation in Higher Education (Nuffic).

In the past, Dyah has worked in a Pharmacy of a suburb area for 5 years. Now, she is working as a Lecturer at the Pharmacy Faculty of Ahmad Dahlan University, Yogyakarta, Indonesia, and also as a drug consultant in the Drug Information Center of Ahmad Dahlan University, Yogyakarta.

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