Pharmacogenetics of antiemetics in Indonesian cancer patients

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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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