Pharmacogenetics of antiemetics in Indonesian cancer patients

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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.