Pharmacogenetics of antiemetics in Indonesian cancer patients

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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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