CYP2C19 Pharmacogenomics–based *Helicobacter pylori* eradication therapy by proton pump inhibitors

Takashi Ishizaki, M.D., Ph.D.

Department of Pharmacology and Therapeutics, Graduate School of Clinical Pharmacy, Kumamoto University, Kumamoto, Japan

Two cytochromes P450 (CYPs), CYP2C19 and CYP3A4, are involved in the metabolism of proton pump inhibitors (PPIs) such as omeprazole, lansoprazole, rabeprazole and pantoprazole. Among these two CYPs, CYP2C19 is a genetically determined polymorphic enzyme, showing an interethnic difference in the incidence of poor metabolizer (PM) phenotypes/genotypes: the frequency of PMs is about 13 to 24% in four Asian (Chinese, Korean, Indonesian and Japanese) populations, being much greater than that (2 to 4%) in American- and European-Caucasian populations. Thus, if the CYP2C19 pharmacogenetic (or pharmacogenomic) entity would have any clinical implication, this entity should be of a more therapeutic concern among the Asian than among the Caucasian Patients.

For the hypothetical reasoning as mentioned above, I and my colleagues have accomplished several studies on PPIs in *H. pylori*-positive Japanese patients as follows: in a study on *CYP2C19* genotype status and dual therapy with omeprazole and amoxicillin for cure rates of *H. pylori* and peptic ulcer healing, cure rates in patients with wt/wt, wt/m1 or wt/m2 and m1/m1 or m1/m2 genotype status were 28.6, 60.0 and 100%, respectively, and ulcer healing rates depended on success or failure of *H. pylori* as well as on the *CYP2C19* genotypic status.

This trend was also confirmed in *H. pylori*- positive patients with gastritis who underwent dual therapy with rabeprazole and amoxicillin. In another study with a PPI (omeprazole or lansoprazole), amoxicillin and clarithromycin (a triple therapy) in 261 Japanese patients with *H. pylori*- positive peptic ulcer, we have observed that the majority of patients without initial eradication of *H. pylori* had the homozygous extensive metabolzer (hom EM) *CYP2C19* genotype, but these hom EM patients were successfully re-treated with a high-dose lansoprazole and an antibiotic to which *H. pylori* was sensitive, such as amoxicillin, even when the patients were infected with clarithromycin-resistant strains of *H. pylori*. In addition, we have recently observed that cure rates of gastroesophageal reflux disease (GERD) depended

not only on the *CYP2C19* genotype status but also on the pre-treatment grades of GERD during the treatment with lansoprazole.

Based upon our findings as presented above. I wish to propose a pharmacogenetic- (or pharmacogenomic-) based tailor-made therapeutic strategy for peptic ulcer or GERD in our future clinical practice. Lastly, because the lowest therapeutic success for eradicating *H. pylori* infection was observed in patients with hom EM genotype of CYP2C19 who more often showed a nocturnal acid breakthrough, a histamin 2 (H_2-) receptor antagonist like famotidine, instead of a PPI, should be re-evaluated for the hom EM patients with peptic ulcer or GERD.