Pharmacogenomics in Clinical Practice

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Scope of the lecture:
Pharmacogenomic (PGx) approach, which explains the individual variability of pharmacokinetics and/or clinical response by genetic polymorphisms of pharmacokinetic enzymes and transporters, has attracted attention to realize the individualized medication. The individualized dosing guidelines for "actionable genomic variants" were provided by some databases for the pharmacogenomics information about various pharmacokinetic enzymes and transporters, such as The Pharmacogenomics Knowledgebase (PharmGKB) and The Ubiquitous Pharmacogenomics (U-PGx). On the other hand, clinical implementation of pharmacogenomics is not performing successfully in Japan. In this session, we would like to introduce the clinical implementation in Japan, our outreach activities and clinical pharmacogenomics studies in our hospital.

Learning objectives:
1. Clinical implementation of pharmacogenomics in Japan
2. Clinical pharmacogenomics service in Shiga University of Medical Science Hospital
3. Pharmacogenomic studies in clinical practice

Extended abstract:
1. Clinical implementation of pharmacogenomics in Japan
   In Japanese clinical setting, only a few PGx approach is covered by official insurance system, such as *UGT1A1* polymorphisms for irinotecan, an anti-cancer drug. Althrough it is not covered by official insurance system, a lot of drugs, such as *CYP2C19* polymorphisms for clopidogrel to antiplatelet therapy and proton pump inhibitors to Helicobacter pylori (H. pylori) eradication, have some pharmacogenomic information in their drug labels. However, many clinical institutes in Japan could not construct the routine pharmacogenomics testing system, because of less coverage by the official insurance system, and ethical problems for genomic information. Therefore, clinical implementation of pharmacogenomics is not performing successfully in Japan.

2. Clinical pharmacogenomics service in Shiga University of Medical Science Hospital
   To improve these situations, clinical pharmcogenomic testing service has been undertaken from 2014 in Shiga University of Medical Science Hospital. The combination of genomic polymorphisms and drugs, which listed in Japanese Pharmaceuticals and Medical Devices Agency (PMDA) or American Food and Drug Administration (FDA) drug labels, were measured at Department of Pharmacy in our hospital. The obtained genetic information and the recommended dose are shared with doctors and other medical professionals by medical chart system. In this session, we would like to introduce the construction method of our clinical pharmcogenomic testing service system and the state of implementation of the system.

3. Pharmacogenomic studies in clinical practice
   In addition to clinical implementation of pharmacogenomics, we have also conducted the following pharmacogenomic studies.

3.1. Vonoprazan, a first-in-class potassium-competitive acid blocker

Vonoprazan is mainly metabolized by CYP3A4/5. Therefore, exposure level of vonoprazan is not influenced by genetic polymorphisms of *CYP2C19*, which cause an inter-individual variability in H. pylori eradication by traditional proton pump inhibitors. However, there is no information of *CYP3A4/5* genetic polymorphisms. Our study has revealed that H. pylori eradication rates in *CYP3A5*1/*1* or **1/*3* types were 72.7% (54.5–86.7%), which was significantly lower than in the **3/*3* type (90.7%, 77.9– 97.4%, $P < 0.05$) with first-line treatment. We first showed that *CYP3A5* genotype was a positive prognostic factor for efficacy of first-line vonoprazan-containing eradication therapy. In addition, we suggest that *CYP3A5*-genotyping-based tailored therapy will be effective in all H. pylori-positive patients.

3.2. Apixaban, a direct oral anticoagulant

Apixaban is mainly metabolized by CYP3A4/5 and transported by ABCB1 (P-glycoprotein) and ABCG2 (breast cancer resistance protein). Our study has reported that the plasma trough concentration/dose ratio of apixaban was significantly higher in patients with the *ABCG2* c.421A/A genotype or the *CYP3A5*1/*3* or **3/*3* genotype than in patients with the *ABCG2* c.421C/C genotype or the *CYP3A5*1/*1* genotype ($P < 0.05$). On the other hand, no ABCB1 polymorphisms affected the plasma trough concentration/dose ratio of apixaban. After adjustment of multivariate analysis, *ABCG2* c.421C>A polymorphism, *CYP3A5*3* polymorphism and renal function were significant determinants of apixaban concentration. These findings provide useful information for dosage adjustments of apixaban to avoid the risk of adverse reactions.

References

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2. Ueshima S, Hira D, et al., Pharmacogenet Genomics, 27(9) 329-336, (2017).