Preface

The Cutting-edge of Clinical Therapeutics Based on Pharmacokinetic/Pharmacodynamic Theory

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PK/PD (pharmacokinetic and pharmacodynamic) theory has evolved to allow for the evaluation and prediction of drug efficacy and safety in the living body. Considerable progress has been made in PK/PD modeling for various types of drugs integrated with systems-biology and physiology. The previous theme issue focused on mechanism-based PK/PD, and provided successful examples of the application of PK/PD theory to predict the effect of toxicity of drugs in pre-clinical studies and exploratory drug development (volume 24, number 1). Therefore, a future challenge would be to apply PK/PD theory to clinical practice and guidelines for drug therapy in order to achieve “the appropriate administration of drugs in the clinic,” which is one of the missions of JSSX. This theme issue focuses on current topics in the clinical application of PK/PD theory, and invited three groups of authors, world-leading scientists, to discuss the recent development and application of PK/PD theory in clinical therapy.

When the therapeutic PD window is quantitatively characterized in patients, population PK analysis becomes a powerful tool to evaluate drug efficacy and safety. Although individual variability of PK can be considered as one of the problems in clinical therapy, several approaches to overcome the problem have been proposed. First, a review article from the laboratory of Dr. Alexander A. Vinks (Cincinnati Children’s Hospital Medical Center, USA) summarizes current approaches using pharmacometrics to optimize the clinical therapeutic efficacy of mycophenolic acid, which is a typical drug for demonstrating complex PK and large inter- and intra-patient PK variability. He and his colleagues have shown the usefulness of population PK analysis using non-linear mixed effect modeling or nonparametric modeling, and physiologically-based PK modeling, with Bayesian algorithm based sampling strategies, for the optimization of the drug therapy toward personalized medicine.

In PK/PD modeling, it is necessary to determine the relationship between the concentration of drug at the target site and pharmacological effect. However, there are some drugs without information about specific target molecules and the exact mechanism of pharmacological action though their effectiveness has been proven in clinical practice. In such cases, the relationship and criteria related to PK/PD need to be established by comparing the outcome obtained in clinical therapy with several biomarkers including genetic polymorphism to regulate the response and disposition of the drug, in addition to the concentration of drug and/or metabolites in biological fluids. Such drugs include methotrexate, which is commonly used to treat rheumatoid arthritis. The research group of Dr. Hiroaki Yuasa (Nagoya City University, Japan) focused on the roles of several transporters of methotrexate and has shown their promising roles as determinants to modulate the PK/PD of methotrexate, providing recent information about drug-drug interactions and individual variability of efficacy and toxicity associated with genetic polymorphism.

Dosing regimen for patients with a specific disease is generally based on the outcome from clinical trials, and subsequently applied to clinical therapy as “evidence-based medicine.” So far, the randomized controlled trial has become the standard protocol in clinical studies to avoid a selection bias in the allocation of patients. However, such attention has been solely paid in the assignment of patients to groups, not in the criteria for patient inclusion. Drs. Ken-ichi Fujita and Yasutsuna Sasaki (Showa University, Japan) have addressed the problems associated with the bias of PK/PD caused by exclusion of patients under a wide variety of physiological and pathological status such as organ dysfunction, obesity and advanced age in cancer clinical trials. They also discuss the importance of assessment of PK/PD of cancer drugs in “real world” cancer patients by showing the cases of irinotecan and S-1 in clinical pharmacological studies.

We sincerely hope that the review articles in this theme issue will be useful for the readers of DMPK to better understand the current research in the field of PK/PD, and to recognize the problem in optimizing drug therapy for individual patients based on PK/PD theory. Finally, we sincerely would like to acknowledge all the authors of three review articles, who generously accepted our invitation to contribute to this theme issue in DMPK.

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