ADME research in drug development of anti-cancer agents
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With recent advances of ADME research in the field of drug discovery, the number of compounds of which development failed due to unsatisfactory ADME characteristics has decreased. In recently approved anticancer drugs, however, there are many drugs with undesirable pharmacokinetic characteristics. Those include drugs which are metabolized by a single enzyme through a single pathway or inhibit CYP activities. Although little is known about details of development of these drugs, this may be attributed to the fact that the development of anticancer drugs is mainly affected by efficacy and toxicity rather than by ADME characteristics.

Clinical efficacy of the anticancer drugs is demonstrated by not response rates but prolongation of overall survival, a primary endpoint in phase III clinical trials. Anticancer drugs, including molecular targeting drugs, generally cause various adverse events, and occurrence of serious adverse events sometimes hinders continuation of drug treatment to the patients, resulting in failure to exhibit prolongation of overall survival even though the size of tumors is reduced. There are drugs like sorafenib, a drug for the treatment of renal cell carcinoma, which improves progression free survival rate while it has a response rate of only approximately 4%.

Pharmacokinetics is usually assessed in phase I clinical studies which are conducted mainly to evaluate toxicity and to determine recommended doses of the drugs for phase II studies. Since pharmacokinetic studies are invasive and hardly beneficial for the treatment of the patients, they often raise ethical problems. However, the rationale of dosage and dose regimen setting is key factors for success in subsequently large-scale clinical studies. In the development of anticancer drugs, dosage and dose regimen setting may be one of the fields pharmacokinetic research contributes to.

We have developed TS-1, an oral 5-FU anticancer drug. In Japan, TS-1 therapy in combination with cisplatin is approved as a first line therapy for advanced recurrent gastric cancer. On the other hand, TS-1 has not been approved in U.S. since combination therapy with TS-1 and cisplatin failed to demonstrate superiority in prolongation of overall survival over combination therapy with 5-FU and cisplatin, although TS-1 therapy was proved to be noninferior to the therapy with 5-FU. In this symposium, the focus will be on involvement of pharmacokinetic research in TS-1 development and a role of pharmacokinetic research in development of anticancer drugs will be discussed.

References:

Biography
Kunihiro Yoshisue, PhD has been a research scientist in Pharmacokinetics Research Laboratory, Taiho Pharmaceutical Co., Ltd. Since 1992. He received his PhD from Kyushu University in 2002. He was a research fellow at University of Tokyo (2002 ~ 2005). He has authored/co-authored some papers about ADME research of the antimetabolite drug.