Poster

[P26-7] P26-7: Oncologic drugs (3): Pharmaometrics, PK/PD, special population

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[P26-7-4] Population pharmacokinetic-pharmacodynamic model of 5-fluorouracil for evaluation of myelosuppression and body weight loss

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Keywords: pharmacokinetic-pharmacodynamic model, population analysis, anticancer agents, myelosuppression, toxicity

Background

5-Fluorouracil (5-FU) is the key anticancer drug for the treatment of patients with colorectal cancer. High inter- and intra-individual variations in 5-FU plasma concentration, treatment outcomes, and severe toxicities, such as myelosuppression, are yet to be investigated, and these variations could contribute to treatment failure. In the current study, we developed a population pharmacokinetic–pharmacodynamic (PK-PD) model to evaluate the inter- and intra-individual variability in the plasma 5-FU concentration, 5-FU-induced myelosuppression, and body weight loss using rats.

Methods

To develop the population PK-PD model, 5-FU plasma concentration, blood cell counts, and body weight loss after intravenous administration of various doses of 5-FU for 4 days to rats were used as source data. PK-PD model for myelosuppression was adapted from our previously established semi-physiological model [Xenobiotica, 44(9), 804-818, 2014; Eur. J. Drug Metab. Pharmacokinet., in press]. An indirect response model was used to describe the entire time course of alterations in 5-FU-induced body weight loss. Population PK-PD modeling was performed using Phoenix® NLME version 1.2 software (Pharsight Co., Mountain View, CA).

Results

The PK-PD model, consisting of a two-compartment model with Michaelis–Menten elimination kinetics, effectively characterized the individual time-course of alterations in 5-FU plasma concentration, blood cell (erythrocyte, leucocyte, and lymphocyte) counts, hemoglobin concentration, hematocrit level, and body weight loss in rats. Final population PK-PD parameters were estimated with high certainly. The inter-individual variability (ω) of the drug effects in the PD model for lymphocyte and body weight loss was 50.1% and 82.6%, respectively, which was relatively higher than that of PK parameters including peripheral volume of distribution (V_2: 47.5%) and maximal rate of saturable metabolism (V_{max}: 8.1%). The results of the current study suggest that the individual fluctuations in the 5-FU concentration and cell sensitivity would affect the onset and degree of myelosuppression.

Conclusions

The developed population PK-PD model could be used to evaluate the inter- and intra-individual variability of drug-induced toxicities including myelosuppression and may contribute to the investigation of

personalized therapeutic strategies.