Poster

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

Chair: Shiro Fukumori, Japan

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[P26-7-2] Mechanism-based pharmacokinetics and pharmacodynamics neutropenia model for irinotecan hydrochloride considering UGT1A1 genotyping

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Keywords: irinotecan hydrochloride, UGT1A1 genotyping, Mechanism-based PK/PD, neutropenia model

Background

Irinotecan-induced severe neutropenia is associated with homozygous for *UGT1A1*6* or **28* allele and those compound heterozygous for *UGT1A1*6* and *UGT1A1*28* allele. Patients with the *UGT1A1*28* and/or *UGT1A1*6* allele need to decrease irinotecan in a startinging dose. In this study, we developed PK/PD neutropenia model combined with UGT1A1 genotyping in the FOLFIRI regimen including CPT-11.

Methods

We identified wild type and mutation type patients who received FOLFIRI regimen at Tokyo Women's Medical University Hospital between November 2008 and September 2016. Genomic DNA was extracted from peripheral blood using a QIAamp blood kit. An Invader UGT1A1 Molecular Assay kit (Third Wave Technologies, Madison, WI, USA) was used to genotype the *UGT1A1*28* and *UGT1A1*6* polymorphisms. The pharmacokinetic parameters of CPT-11 were simulated from reference data using Phoenix NLME, acomponent of WinNonlin ver. 7.0 (Pharsight Corporation, Mountain View, CA). We selected CPT-11 and SN-38 PK data building covariate of weight.

Results

Mechanism-based PK/PD neutropenia model was constructed and the clearance of SN-38 was decreased in patients with genetic mutation type.

Conclusions

Irinotecan would be very risky in patients who have two alleles of *UGT1A1*28* and/or *UGT1A1*6* because of decreasing clearance of SN-38.