Poster

[P26-8] P26-8: Oncologic drugs (4): Pharmacokinetics, TDM practice

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[P26-8-5] Pharmacokinetic analysis of irinotecan and its metabolite to evaluate UGT1A1 and CYP3A activities in patients with UGT1A1 gene polymorphism

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Keywords: irinotecan, pharmacokinetics, compartment model

Background

Irinotecan (CPT-11) is metabolized by carboxylesterase to an active metabolite SN-38, which is then converted to an inactive metabolite SN-38G by UGT1A1. *UGT1A1* genetic polymorphism and SN-38G/SN-38 AUC ratio have been associated with altered SN-38 pharmacokinetics, which increases the risk of toxicity in patients. CPT-11 is also converted to two oxidative metabolites, APC and NPC, by CYP3A. It is important to evaluate the conversion ratios of CPT-11 to APC and NPC because CYP3A activity has large individual variability. In this study, we calculated pharmacokinetic parameters from the plasma concentration of CPT-11 and its metabolites (SN-38, SN-38G, APC, NPC) in three patients with *UGT1A1* gene polymorphism to evaluate UGT1A1 and CYP3A activities.

Methods

Three patients aged 49-65 years were recruited for the analysis. All patients had *UGT1A1*6/*6* or **6/*28* genetic polymorphisms and received FOLFIRINOX. The administered dose of CPT-11 was 80 or 100 mg/m^2. Blood samples were collected for pharmacokinetic analysis of CPT-11 after 0, 0.25, 0.5, 1, 2, 3, 4, 8, 24, and 48 h of infusion. The rate constant and AUC ratio for evaluating UGT1A1 and CYP3A activity were determined by WinNonlin version 6.4. The study was approved by Kyorin University Faculty of Medicine and Tokyo University of Pharmacy and Life Sciences Human Subjects Review Board, and written informed consent was obtained.

Results

The plasma levels of CPT-11 were 999-1265 ng/mL at peak and 22.5-29.7 ng/mL after 48 h of infusion. The concentration range of SN-38, SN-38G, APC, and NPC was 0.1-74.2 ng/mL. The rate constant of conversion of SN-38 to SN-38G was 0.55-1.11 h^{-1}, and the SN-38G/SN-38 AUC ratio was 1.87-7.44 in the three patients. Patients with low UGT1A1 activity developed neutropenia. The rate constant of conversion of CPT-11 to APC+NPC was 0.032-0.052 h^{-1} and the CPT-11/(APC+NPC) AUC ratio was 0.07-0.17 in the three patients.

Conclusions

The rate constant of conversion of SN-38 to SN-38G and CPT-11 to APC+NPC, which indicates the activity of UGT1A1 and CYP3A, varied greatly among patients with *UGT1A1* gene polymorphism. Thus, pharmacokinetic analysis of the plasma concentration of CPT-11 and its metabolites can provide useful information on minimizing the risks of therapy.