SEVERE RENAL FAILURE REQUIRING DIALYSIS CAUSES DELAYED ELIMINATION OF SN-38 IN CANCER PATIENTS WHO RECEIVE IRINOTECAN

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[Purpose] We examined the effects of severe renal failure on the pharmacokinetics of irinotecan, SN-38, and SN-38 glucuronide (SN-38G).

[Methods] The pharmacokinetics of irinotecan, SN-38, and SN-38G in 3 cancer patients with severe renal failure (creatinine clearance [Ccr] ≤ 20 mL/min) who were undergoing dialysis and received 100 mg/m² irinotecan as monotherapy were prospectively compared with those in 5 cancer patients with normal renal function (Ccr ≥ 60 mL/min). To ensure that the subjects had similar genetic backgrounds with respect to UGT1A1, only patients with UGT1A1*1/*1, *1/*6, or *1/*28 were enrolled.

[Results and Discussion] The terminal elimination rate constant of SN-38 in patients undergoing dialysis was about one tenth that in patients with normal renal function (P=0.025). About 50% of SN-38 was dialyzed with a 2.1-m² dialysis membrane, whereas 27% was dialyzed with a 1.5-m² membrane.

[Conclusions] Our results showed that the elimination of SN-38 was significantly delayed in patients with severe renal failure as compared with patients with normal renal function. We also demonstrated that SN-38 was partly dialyzed.

CLINICAL PHARMACOKINETICS OF ERLOTINIB AND ITS ACTIVE METABOLITE OSI-420 IN PATIENTS WITH NON-SMALL CELL LUNG CANCER

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[Purpose] Erlotinib is an orally active EGFR tyrosine kinase inhibitor, currently used for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC). Erlotinib is extensively metabolized in the liver by the CYP3A subfamily to produce an active metabolite OSI-420. Since erlotinib has severe toxicities such as interstitial lung disease (ILD), the chemotherapy with erlotinib should be optimized by individualizing dosage regimen. The aim of this study was to investigate the clinical pharmacokinetics of erlotinib/OSI-420 and exposure-safety relation.

[Methods] A total of 38 patients with NSCLC receiving erlotinib (150 mg/day) were enrolled in this study. Serial blood samples were collected on days 1 and 8. We also obtained trough blood samples on other days if necessary. Plasma concentrations of erlotinib and OSI-420 were measured by high-performance liquid chromatography. Data on patient characteristics and adverse events were collected retrospectively from medical records.

[Results and Discussion] Erlotinib and OSI-420 showed large interindividual variability in drug exposure. The AUC metabolic ratio (OSI-420/erlotinib) significantly increased on day 8. One patient with the highest Cmin of erlotinib (5.0μg/mL) on day 8 experienced diarrhea and severe rash, consequently the dose was reduced to 50 mg/day. Furthermore, the trough levels of erlotinib in patients with suspected ILD (n=2) tended to be increased on the day of the event.

[Conclusions] Therapeutic drug monitoring of plasma erlotinib concentration may help to prevent adverse events.