UFT-induced myelosuppression and its pharmacokinetic-toxicodynamic model in rats

Megumi Matsui, Shinji Kobuchi, Yukako Ito, Toshiyuki Sakaeda

Pharmacokinetics, Kyoto Pharmaceutical University, Japan

[Background] UFT is an oral preparation combining the 5-fluorouracil (FU) prodrug tegafur (FT) and uracil (Ura) in a 1:4 ratio, and used for the treatment of colorectal cancer. In UFT/LV regimen, myelosuppression is a critical factor that limit the UFT dosage and causes many clinical complications, such as delays or discontinuation of subsequent schedules of UFT/LV regimen. To avoid the sever myelosuppression, pharmacokinetic-pharmacodynamic (PK-PD) model is a valuable tool for estimating time course profile of blood cell counts after UFT administration. In this study, a relationship between the plasma concentration of drugs and myelosuppression were investigated in rats after administration of UFT, and PK-PD model was established.

[Methods] In PK study, UFT (FT: 15, 30, or 60 mg/kg) was orally administered to Male Wister rats (10 weeks of age). Blood samples were collected after UFT administration and plasma concentrations of FT, FU, and Ura were evaluated. In PD study, UFT was orally administrated for 5 days at the same dosage in PK study and blood cell (leucocyte, platelet, lymphocyte and neutrophil) counts were evaluated on Day 0, 3, 7, 10, 14, 21 and 28. The PK-PD model was developed using the semi-mechanistic myelosuppression model reported by Friberg et al. [1] with some modification, and performed using WinNonlin® Version 6.4 software.

[Results] The area under the plasma concentration-time curve (AUC_{0-24h}) of FT, FU and Ura was increased and the nadir neutrophil counts were decreased depending on the dosage. The nadir neutrophil counts in rats administered 15, 30, or 60 mg/kg UFT were 14.8 ± 2.0 , 13.8 ± 2.2 , and 4.7 ± 2.4 ($10^2/\mu L$) on Day 7, respectively. The rebound of neutrophil counts over the baseline value was observed Day 14 in rats administered 60 mg/kg UFT and returned to the baseline on Day 28. The developed PK-PD model successfully described the time course profile of neutrophil counts after administration of UFT to rats.

[Conclusions] These results suggest that the monitoring of counts with PK-PD model could estimate the onset and degree of the myelosuppression in UFT/LV regimen and could contribute to develop the therapeutic strategies in patients.

[Reference] Friberg LE et al. J Clin Oncol 20(24):4713-21, 2002.