Supplementary information

Mathematical description of quantitative system toxicology models

The mathematical description of developed quantitative system toxicology models for irinotecan induced gastrointestinal (GI) adverse events (AEs) in rats was shown hereafter. The schematic description of quantitative system toxicology model and pharmacokinetic models in rats is found in Figure 1 and Supplemental figure 1(A), respectively. Parameter values were found in Table 1.

$$dA1/dt=ka*D1-(Vmax/(km+A1/V1)+CL)*A1/V1-Q/V1*A1+Q/V4*A4 \quad (1)$$

$$dA4/dt=Q/V1*A1-Q/V4*A4 \quad (2)$$

$$d/X2dt=-ka*X2 \quad (3)$$

$$dB3/dt=kam*X5+(Vmax/(km+A1/V1)+fm,lin*CL)*A1/V1-CLm/Vm*B3 \quad (4)$$

$$dX5/dt=-kam*X5 \quad (5)$$

$$F2=1-Dmaxp/(Dmp+Dose) \quad (6)$$

$$F5=Dmaxm/(Dmm+Dose) \quad (7)$$

$$dSC/dt=k1*SCss*fdbc-k1*SC-kill*SC*((SCss/SC)^{hill}) \quad (8)$$

$$dPPC1/dt=k1*SC-k2\ *PPC1-kill*PPC1*((SCss*(k1/k2)/PPC1)^{hill}) \quad (9)$$

$$dPPC2/dt=2*k2*PPC1-k2*\ PPC2-kill*PPC2*((2*SCss*(k1/k2)/PPC2)^{hill}) \quad (10)$$

$$dPPC3/dt=2*k2*PPC2-k2\ *PPC3-kill*PPC3*((4*SCss*(k1/k2)/PPC3)^{hill}) \quad (11)$$

$$dPPC4/dt=2*k2*PPC3-k2*PPC4-kill*PPC4*((8*SCss*(k1/k2)/PPC4)^{hill}) \quad (12)$$

dENT1/dt=2*CV*k2*PPC4-k3*ENT1 (13)

dENT2/dt=k3*(ENT1-ENT2) (14)

dENT3/dt=k3*(ENT2-ENT3) (15)

dENT4/dt=k3*(ENT3-ENT4) (16)

dENT5/dt=k3*(ENT4-ENT5) (17)

killPPC=kkill*B3/Vm/1000/(1+Tol4/Vm*tol) (18)

$fdbc=(1/ENTresf)^{gam}$ (19)

ENTresf= (ENT1+ENT2+ENT3+ENT4+ENT5)/(16*SCss*(k1/k3)*CV)/5 (20)

dCit/dt=ENTresf*kout*BL-kout*Cit (21)

dTol1/dt=kt*(B3-Tol1) (22)

dTol2/dt=kt*(Tol1-Tol2) (23)

dTol3/dt=kt*(Tol2-Tol3) (24)

dTol4/dt=kt*(Tol3-Tol4) (25)

Initial conditions

A1=A2=B3=0, X2=F2*Dose, X5=(1-F2)*F5*Dose

SC = SCss, PP1 = SCss*(k1/k2), PP2 = 2*SCss*(k1/k2), PP3 = 4*SCss*(k1/k2), PP4 = 8*SCss*(k1/k2), ENT1=ENT2=ENT3=ENT4=ENT5=16*SCss*(k1/k3)*CV

Cit = BL, Tol1= Tol2= Tol3= Tol4=0

A: irinotecan amount, B: SN-38 amount, X: dose amount, F: fraction available, SC: stem cell, PPC: proliferative progenitor cells, fdbc: feedback, ENT: enterocyte, ENTresf: residual fraction of enterocyte, Cit: citrulline, Tol: transit compartment for tolerance development.

The quantitative system toxicology model for humans is the same as that for rats except for 1) the PK model for irinotecan and SN-38 was replaced with the published human PK model,[1] 2) number of transit compartments for proliferative progenitor cells are 5 and 3) tolerance was removed. The schematic description of pharmacokinetic models in humans is found in Supplemental figure 1(B). Parameter values were found in Table 2.

References

1. Klein CE, *et al*. Population pharmacokinetic model for irinotecan and two of its metabolites, SN-38 and SN-38 glucuronide. *Clin Pharmacol Ther* **72** 638-647. (2002)

Supplemental figure legends

Figure S1 Schematic description of the pharmacokinetic (PK) models for irinotecan and SN-38. A) PK model for rats, B) PK model for human.[1]

Figure S2 The visual predictive check analyses for population toxicokinetic model analysis of irinotecan and SN-38 after irinotecan treatment in rats. The observed and model simulated plasma concentration-time profiles was plotted for irinotecan and SN-38 after single (12.5, 25, 50 or 100 mg/kg) and multiple (6.25 or 25 mg/kg in twice a week (BIW) and 1.8 or 7.2 mg/kg in once daily (QD) dose schedules) administration of irinotecan in rats. A) and B) irinotecan on day 1 and day 4, C) and D) SN-38 on day 1 and day 4. In each panel, circles, a line and a shaded area represent the observed data (n=3), the model predicted population mean and the 90 percentiles of individual model predicts, respectively.

Figure S3 Scattered plots of individual system toxicology model parameters with random effect and dose. The correlation of individual parameters (Vmax, Dmaxp, CLm and BL) and their dose-dependency were plotted.

Figure S4 The incorporation of tolerance development improved the goodness of fit to the observed plasma citrulline profiles after multiple doses of irinotecan to rats. The observed and model simulated plasma citrulline concentration-time profiles were plotted after multiple administrations of irinotecan (25 mg/kg in BIW and 7.2 mg/kg in QD) in rats by the system toxicology model A) with tolerance development or B) without it. In each panel, symbols, error

bars and lines represent the mean observed data (n=3), standard deviation and the model predicted population mean, respectively. The purple and orange arrows on the x-axis represent dose timing.

Figure S5 Local sensitivity analysis for the system toxicology model in rats. The integrated sensitivity indices represent the sensitiveness of plasma citrulline to the change of each parameter. The indices were calculated at a single dose of irinotecan at 25 mg/kg to rats by integrating the time-dependent sensitivity indices throughout the time course. The negative sensitivity indices indicated the parameter increase led decreased plasma citrulline level.