A semi-mechanistic pharmacokinetic-pharmacodynamic model of 5-fluorouracil continuous infusion in gastrointestinal cancer patients

Usman Arshad (1), Su-arpa Ploylearmsaeng (1), Mats O. Karlsson (2), Oxana Doroshyenko (1), Dorothee Frank (1), Edgar Schömig (1), Sabine Kunze (3), Semih A. Güner (3), Roman Skripnichenko (3), Sami Ullah (1), Ulrich Jaehde (4), Uwe Fuhr (1), Alexander Jetter (5), Max Taubert (1)

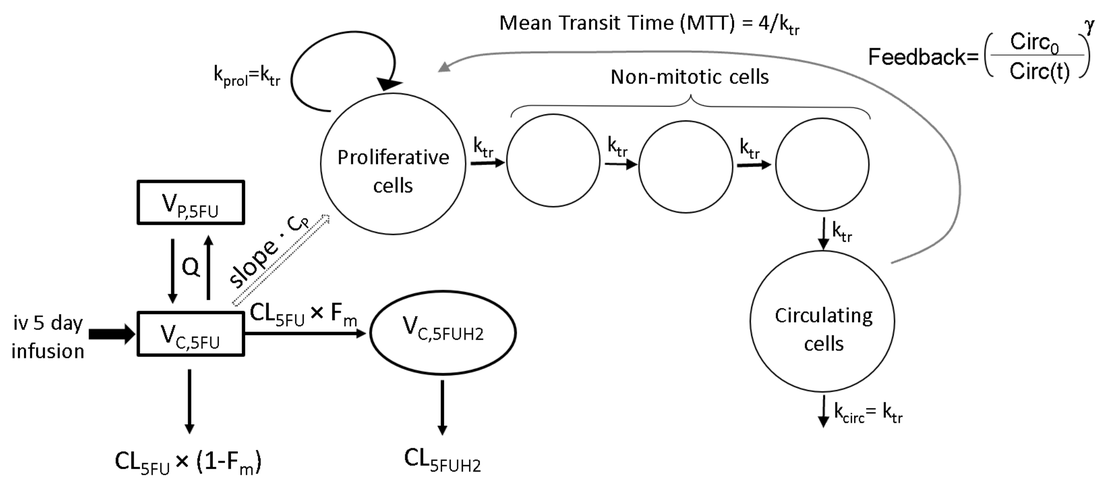
(1) University of Cologne, Faculty of Medicine and University Hospital Cologne, Center for Pharmacology, Department I of Pharmacology, Cologne, Germany. (2) Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden. (3) University of Cologne, Faculty of Medicine and University Hospital Cologne, Department of Radiotherapy, Cologne, Germany. (4) Institute of Pharmacy, Clinical Pharmacy, University of Bonn, An der Immenburg 4, 53121, Bonn, Germany. (5) Department of Clinical Pharmacology and Toxicology, University Hospital Zurich, University of Zurich, Zürich, Switzerland.

Objectives

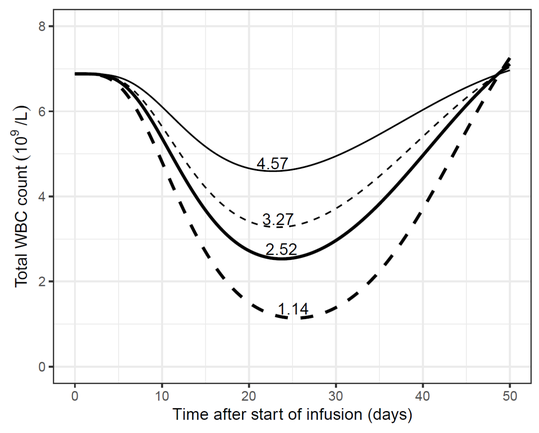
The study was aimed to develop a population pharmacokinetic model of 5-fluorouracil continuous infusion and a semi- mechanistic myelosuppression model to describe the relationship between 5-FU exposure and myelotoxicity. In addition, genetic and non-genetic covariates influencing 5-FU pharmacokinetics and myelotoxicity were explored.

Methods

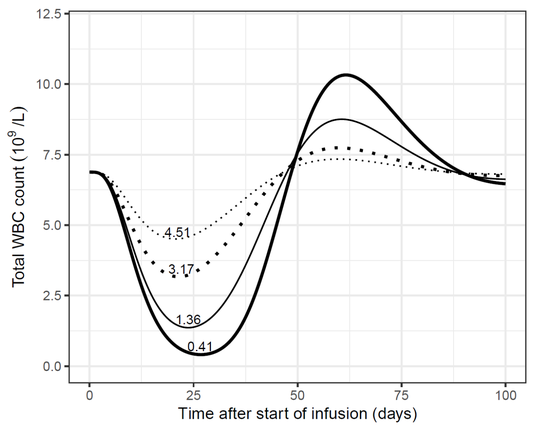
Thirty gastrointestinal cancer patients received 650 or 1000 mg/m^2/day 5-FU for 5-days as continuous venous infusion. Fourteen of these patients were additionally infused with cisplatin 20 mg/m^2/day. Plasma concentrations of 5-FU and its major metabolite 5-fluoro-5,6-dihydrouracil (5-FUH2) were quantified. Absolute leukocyte count (ALC) data was obtained once prior to and 2-3 times after the start of infusion until day 27. Covariate data included patient demographics, baseline laboratory values and information on dihydropyrimidine dehydrogenase (*DPYD),* thymidine synthase (*TS*), and methylene tetrahydrofolate reductase (*MTHFR*) genotypes. Pharmacokinetic parameters for 5-FU and 5-FUH2 were obtained by nonlinear mixed effect modeling using NONMEM. ALC data were described by a semi-mechanistic myelosuppression model driven by 5-FU plasma concentrations. Covariate evaluation was principally guided by physiological plausibility, decrease in objective function value and interindividual variability. Simulations were designed to assess the influence of respective *MTHFR* genotypes, cisplatin co-medication and dosing regimens by predicting the depth (ALC_{nadir}) and time (T_{nadir}) of lowest ALC and the recovery period (T_{rec}) for the reestablishment of ALC.



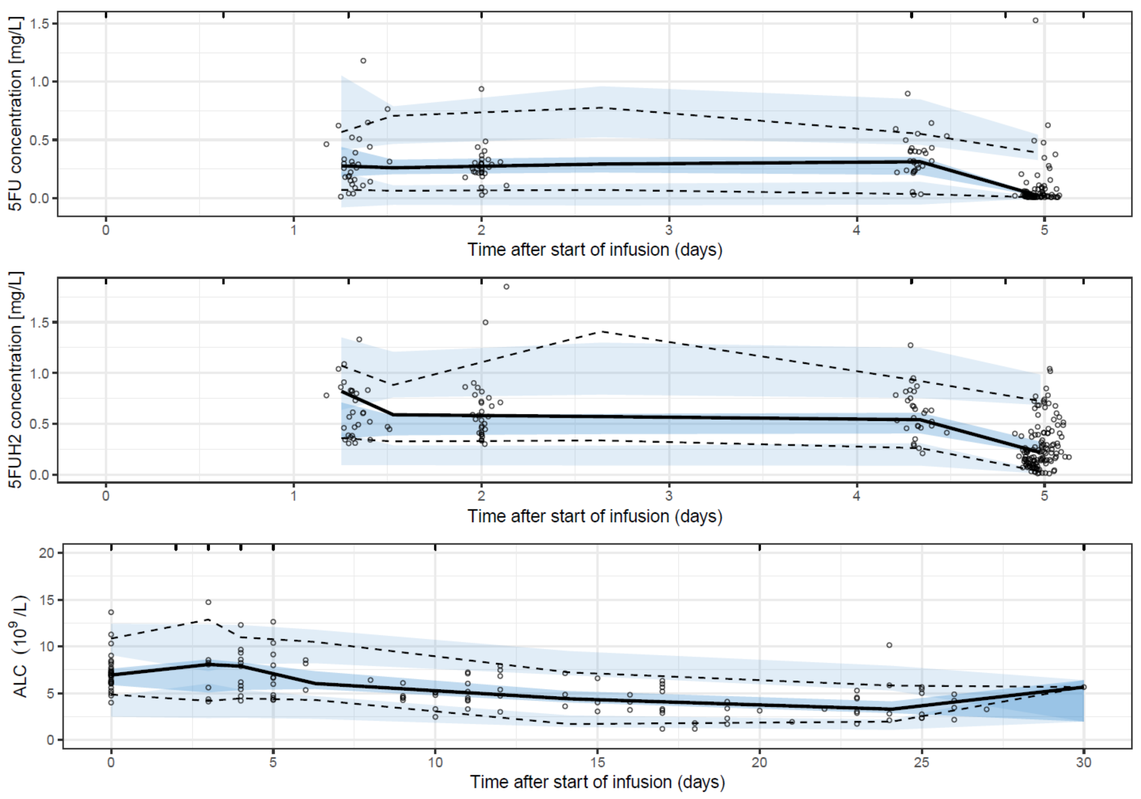
Schematic representation of PKPD model



Simulated ALC over time for *MTHFR* CC/CT (continuous lines) and TT (dashed lines) genotypes. Thick lines represent 5FU monotherapy, thin lines represent combination therapy with 5FU and cisplatin.



Simulated ALC over time attributable to the 5-FU component of the FOLFIRINOX (continuous lines) versus de Gramont (dashed lines) regimen: Thick and thin lines represent individuals with *MTHFR* CC/CT and TT genotypes, respectively.



Visual predictive checks for PKPD model

Results

Plasma concentration-time data were best described by a two-compartment model for 5-FU and one-compartment model for 5-FUH2. BSA and *MTHFR* genotype dependent total plasma clearance of 5-FU was 278 L/h for *MTHFR* 677CT or 677CC and 150 L/h for *MTHFR* 677TT genotype. 5-FU central and peripheral volumes of distribution were estimated to be 5.78 L and 39.6 L, respectively. Estimates for 5-FUH2 clearance and volume of distribution were 119 L/h and 91.9 L, respectively. A fractional deviation of 66% (L/h) per m^2 from the median BSA was observed for 5-FU and 5-FUH2 clearance. ALC over time was appropriately described by the semi-mechanistic myelosuppression model with three transit compartments accounting for a delay between drug administration and the observed toxicity [1]. Baseline leukocyte count ($Circ_0$) and mean leukocyte transit time (MTT) were estimated as 6.88×10^9/L and 280 h, respectively.

Pharmacodynamic parameters

Parameter	Estimate	
	Median	95% CI
$CIRC_0$ ($\times 10^9$/L)	6.88	6.28-7.49
MTT (h)	280	205-377
$Slope_{comb}$ (L/mg)	2.82	1.05-4.90
$Slope_{mono}$ (L/mg)	1.12	0.72-1.71
γ	0.17	Fixed
IIV		
$CIRC_0$ (% CV)	15.6	6.73-27.0
RUV		
Proportional error (σ^2)	0.29	0.24-0.34

A linear model adequately described the relationship between 5-FU exposure and myelosuppression. A higher degree of myelosuppression was observed in patients receiving additional cisplatin (slope=2.82 L/mg) as compared to patients receiving monotherapy (slope=1.12 L/mg). In addition to cisplatin co-medication, myelosuppression was demonstrated to be higher in subjects with *MTHFR* 677TT genotype due to higher drug exposure. Similarly, a greater degree of toxicity attributable to 5-FU was predicted in virtual subjects receiving the doses of 5-FU suggested in FOLFIRINOX regimen in comparison to de Gramont regimen [2, 3].

Pharmacokinetic parameters

Parameter	Population estimate		IIV (%CV)	
	Median	95% CI	Median	95% CI
5FU				
CL_{5FU}: MTHFR 677CT/677CC genotype (L/h)	278	248-310	14.2	0.58-21.8
CL_{5FU}: MTHFR 677TT genotype (L/h)	150	102-259		
$V_{C,5FU}$ (L)	5.78	2.49-10.9	102	58.6-210
$V_{P,5FU}$ (L)	39.6	16.1-132	-	-
Q: MTHFR 677CT or 677CC genotype (L/h)	16.9	10.2-38.1	-	-
Q: MTHFR 677TT genotype (L/h)	3.83	1.46-14.3	-	-
BSA effect (m^{-2})[a]	0.66	0.38-0.99	-	-
$AUC_{24,5FU}$ (mg h/L)	6.72	4.76-8.74	-	-
$Cmax_{,5FU}$ (mg/L)	0.28	0.20- 0.37	-	-
5FUH2				
F_m (%)	0.85	Fixed	-	-
CL_{5FUH2} (L/h)	119	104-139	28.2	19.8-35.2
$V_{C,5FUH2}$ (L/h)	91.9	61.5-123	51.9	29.1-103
$AUC_{24,5FUH2}$ (mg h/L)	12.2	7.12 - 19.2	-	-
$Cmax_{,5FU}$ (mg/L)	0.54	0.31- 0.83	-	-
Proportional error 5FU (σ^2)	0.57	0.48-0.66	-	-
Proportional error 5FUH2 (σ^2)	0.37	0.30-0.43	-	-

Conclusions

5-FU pharmacokinetics and pharmacodynamics were found to be influenced by hereditary (*MTHFR* genotype) and demographic (BSA) factors. It is desired to further elucidate the role of *MTHFR* C677T genotype in 5-FU disposition. Cisplatin co-medication was found to significantly aggravate myelotoxicity.

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[2] A. De Gramont *et al.*, "High-dose folinic acid and 5-fluorouracil bolus and continuous infusion in advanced colorectal cancer.," *Eur. J. Cancer Clin. Oncol.*, vol. 24, no. 9, pp. 1499–1503, 1988.
[3] L. Deyme, D. Barbolosi, and F. Gattacceca, "Population pharmacokinetics of FOLFIRINOX: a review of studies and parameters," *Cancer Chemother. Pharmacol.*, pp. 1–16, 2018.