PKP-001

INFLUENCE OF GENDER AND BODY SIZE ON 5-FLUOROURACIL PHARMACOKINETICS

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BACKGROUND

- Conventional body surface area (BSA)-based dosing of 5-FU is associated with significant inter- and intra- individual variability in plasma levels of 5-FU.
- Several potential sources of pharmacokinetic variation have been proposed, including pharmacogenetic differences, organ function, disease state, circadian rhythm, and drug-specific factors like schedule of administration and interactions with other drugs and herbal medicines.
- The objective of this study is to evaluate the influence of gender and body size in 5-FU pharmacokinetics.

METHODS

- Retrospective analysis of a prospectively collected database of patients with gastrointestinal cancer receiving 5-FU-based therapy.
- Plasma concentrations of 5-FU were obtained and pharmacokinetic parameters were estimated by Bayesian methodology for individual 5-FU dose adjustment and for evaluate their relationship with gender and body size.

RESULTS

Table 1: Patients demographics.

Sex	No	%
Male	185	73.4%
Female	45	24.5%
Age,years		
mean (SD)	62 (10.81)	
Weight, Kg		
mean (SD)	72.4 (14.47)	
Tumor location		
Pancreas	40	21.7%
Colorectal	91	45.5%
Stomach	35	19.0%
Others	18	9.8%
Chemotherapy regimen		
FOLFOX	87	47.3%
FOLFIRI	47	25.5%
FOLFOXIRI	25	13.6%
FLOT	25	13.6%

Figure 1: 5-FU CL distribution.

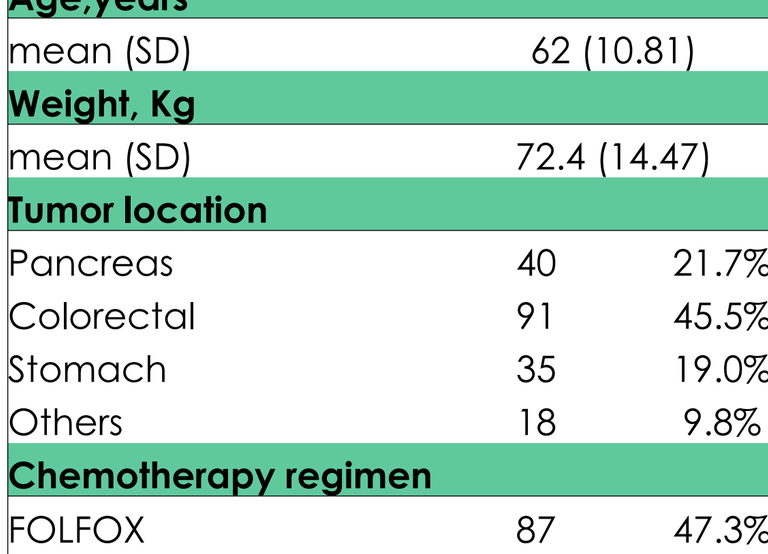


Table 2: Individual pharmacokinetic parameters of 5-FU

Variable	Mean	SD	Min	Max	CV(%)
5-FU CL (L/h)	179.28	48.48	85.48	338.49	27.80%
5-FU CL (L*Kg/h)	96.23	25.46	41.15	191.05	26.45%
5-FU CL (L*m²/h)	2.47	0.73	0.96	5.29	29.69%
AUC (mch*h/mL)	29.02	8.73	11.52	77.80	30.09%
Vd (L)	32.67	6.22	18.47	50.55	19.04%
Vd (L*kg)	0.45	0.06	0.31	0.68	13.33%
$T_{1/2\ (min)}$	7.83	1.14	5.18	11.59	14.39%

CL: clearance; AUC: area under the curve; Vd: distribution volume; SD: stardar desviation; CV: variation coeficient.

Figure 2: 5-FU CL among gender

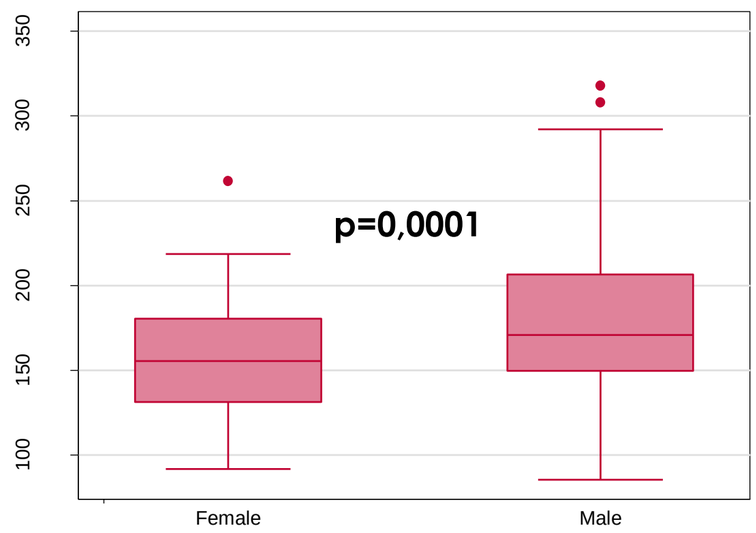
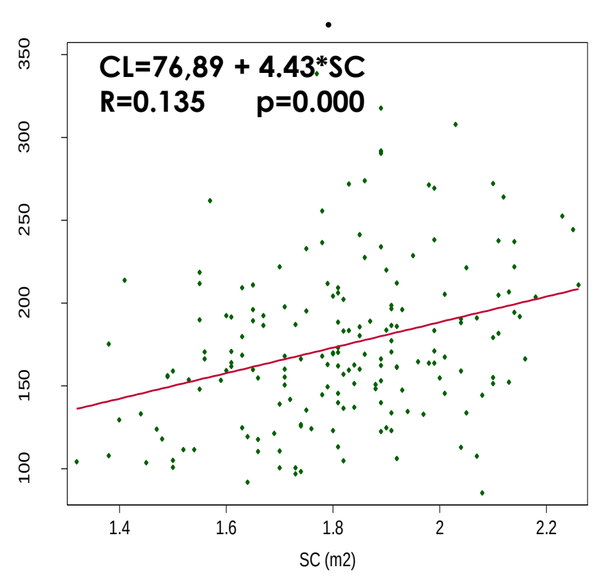


Figure 3: Relationship between 5-FU CL and body size



- Obese patients has a higher CL and Vd than leaner ones (197.3L/h and 38.6L respectably vs 177.3 L/h and 31.9L).
- By contrast we identified a subgroup (n=21) of patients with SC<1.6 and <55Kg, in which 5-FU exposure (AUC) was significantly higher due to the lower 5-FU CL (146 vs 183L/h). 76,2% of this subgroup were females

CONCLUSIONS

- 5-FU pharmacokinetics are notably influenced by body size and gender.
- There is a subgroup of patients, with especially low body size, in which 5-FU elimination is reduced.