PHARMACOKINETICALLY GUIDED DOSE ADJUSTMENT OF 5-FLUOROURACIL (5-FU) IN GASTROINTESTINAL CANCER PATIENTS

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BACKGROUND AND OBJECTIVES

- 5-fluorouracil (5-FU) is a widely used chemotherapeutic drug in gastrointestinal cancer.
- Appropriate dosing of chemotherapeutic drugs is critical to reduce mortality and increase progression-free survival.
- The standard approach for dosing 5-FU is based on body surface area (BSA). However, BSA does not account for many of the factors that are responsible for 5-FU clearance such as age, gender, genotype, disease state, drug-drug interactions, organ dysfunction and co-morbidities.
- Evidence supports a close association between 5-FU exposure (expressed as Area Under the Curve or AUC), efficacy, and toxicity, rather than the dose administered.
- Direct monitoring of 5-FU blood levels with appropriate dose adjustments may represent a more rational approach for 5-FU dosing in order to reduce toxicity and improve clinical outcomes.
- The **aim** of this study is to evaluate the role of therapeutic drug monitoring (TDM) of 5-FU in daily clinical oncology practice.

METHODS AND STUDY DESING

- Prospective study of 54 adult patients with diagnosis of gastrointestinal cancer receiving schedule infusion regimes based on high doses of 5-FU (2.5-3.2g/m^2 in 24-46h infusion) in a university hospital.
- Individual pharmacokinetic parameters were calculated based on anthropometrics and history of 5-FU administration using the Bayesian software program (USC*Pack) and the population data obtained in a previous study.
- Patients were dosed in the first cycle taking in account BSA, and subsequent doses were adjusted to an optimal target AUC of 25-35 mg·h/L, ensuring proper treatment tolerance.

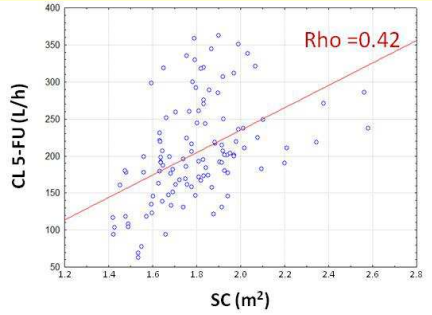
RESULTS

Table 1. Patient demographics and clinical characteristics

Sex	No	%
Male	31	57.41%
Female	23	42.59%
Age,years		
mean (SD)	60.9 (12.8)	
Weight, Kg		
mean (SD)	72.2 (16.9)	
Tumor location		
Pancreas	14	25.93%
Colorectal	26	48.15%
Stomach	11	20.37%
Esophagus	3	5.56%
Disease stage		
I-II	5	9.26%
III	8	14.81%
IV	41	75.93%
ECOG		
0	10	18.52%
1	32	59.26%
2	10	18.52%
Chemotherapy		
FOLFOX[a]	24	44.44%
FOLFIRI[a]	13	24.07%
FLOT	3	5.56%
FOLFOXIRI[a]	14	25.93%

ECOG Easter Cooperative Oncology Group
[a]with or without the addition of monoclonal antibody such as bevacizumab and cetuximab

Figure 1. Distribution of 5-FU plasma clearance vs. BSA .

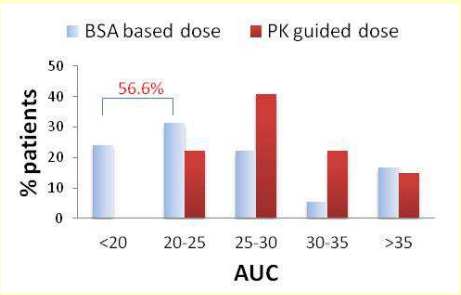


The potencial relationship between body surface area and 5-FU pharmacokinetics has been investigated. There is a weak association between BSA and 5-FU clearance.

Table 2. Pharmacokinetics parameters of 5-FU

	Median	DE	CV(%)
CL (L/h)	202.97	18.58	33.99
Vc (L*Kg)	0.49	0.08	15.55
Ke (h^{-1})	5.77	0.92	16.01
$T_{1/2}$ (min)	7.27	7.34	20.85
Cmax (mcg/mL)	7.23	2.69	37.25
Cee (mcg/mL)	0.59	0.21	35.39

Figure 2. Distribution of AUC for 5-FU during the first course (BSA based dosed) and during the second course (PK guided dose)



Most patients (56,6%) in the first course did not received an optimal dose of 5-FU, and 24.1% of patients had an AUC <20 mg*h/L. In the second course, and to achieve target AUC values, 5 patients (13%) had their doses adjusted downwards, and in 33 patients (86.8%) the dose was adjusted upwards.
Individual 5-FU dose adjustment resulted in significantly improved objective response, particularly in pancreas group, who present a lower 5 FU AUC after standard dosification.

CONCLUSIONS

- BSA-based 5-FU dosing approaches are limited to achieve optimal plasma levels in most patients.
- Pharmacokinetically guided dosing represents a good strategy to improve the efficacy and safety of 5-FU independent of schedule used and type of tumor..