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Therapeutic drug monitoring of 5-fluorouracil: a complementary approach to pre-therapeutic detection of dihydropyrimidine dehydrogenase deficiency to optimize chemotherapy

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Introduction

- **5-Fluorouracil (5FU)** = widely used cytotoxic agent in treatment of digestive cancers
- 80% of 5FU is metabolized to inactive derivatives by the enzyme **dihydropyrimidine dehydrogenase (DPD)**
- Around 10% of patient have **DPD deficiency** (partial of complete) → **risk of severe 5FU toxicity during the first administration**
- Prevention strategy: **pre-therapeutic DPD phenotyping** by measuring plasma uracil (mandatory in France) *(deficiency if plasma uracil ≥ 16 ng/mL)*
- **In case of deficiency**: appropriate starting 5FU dose based on uracilemia ? → **no algorithm** → **empiric dose decreases**
- **Therapeutic drug monitoring (TDM) of 5FU** is recommended: 5FU **exposure** shown to be **associated with toxicity and efficacy** of 5FU in several studies[1,2].
- Studies reported that around 50% of patients have 5FU **exposure below the therapeutic range**

Purpose

The aim of this study was to assess the relationship between DPD phenotype and 5FU exposure during the first cycle (C1) of treatment

Material and Methods

INCLUSIONS

- Digestive cancers
- Chemotherapy regimen including continuous infusion of 5FU
- Inclusion: April 2019 to June 2020
- Patients with 5FU concentration available at C1 (routine follow-up)

DATA

- Pre-therapeutic uracil plasma concentration
- 5FU exposure (evaluated by AUC*) at steady state at C1 (stability of blood sample ensured by DPD inhibitor as stabilizer)
- Demography: age, sex, weight
- Chemotherapy regimen, dose of 5-FU continuous infusion at C1, DPYD genotype if available

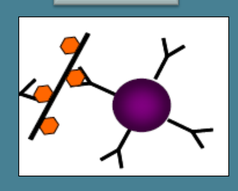
**AUC: area under the curve of concentration vs time*

INSTRUMENTAL METHODS

URACIL

LC|MS

5FU



Immunoassay (« My5FU » Saladax® [3])

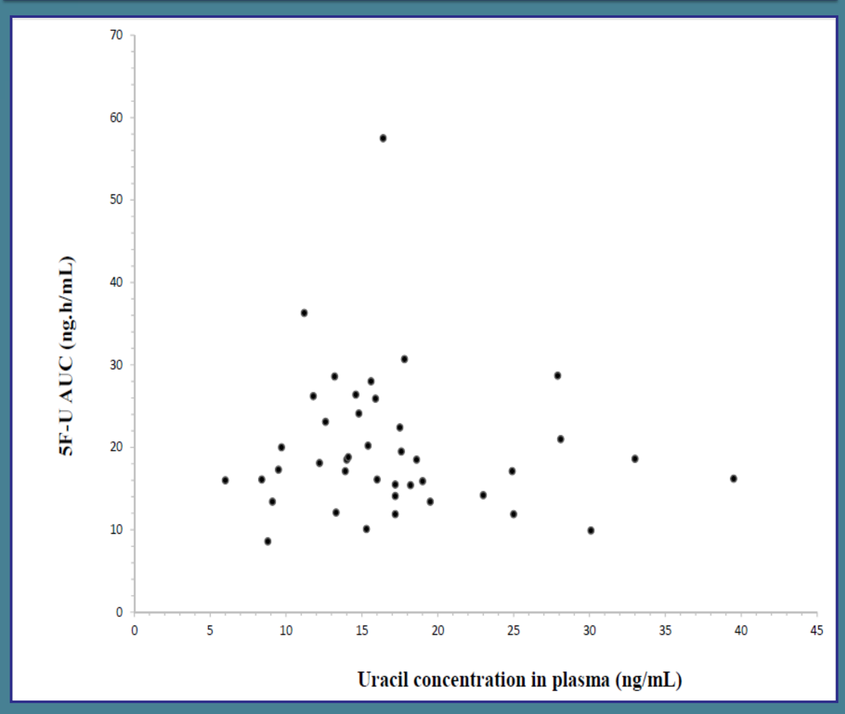
Results

N=42 subjects

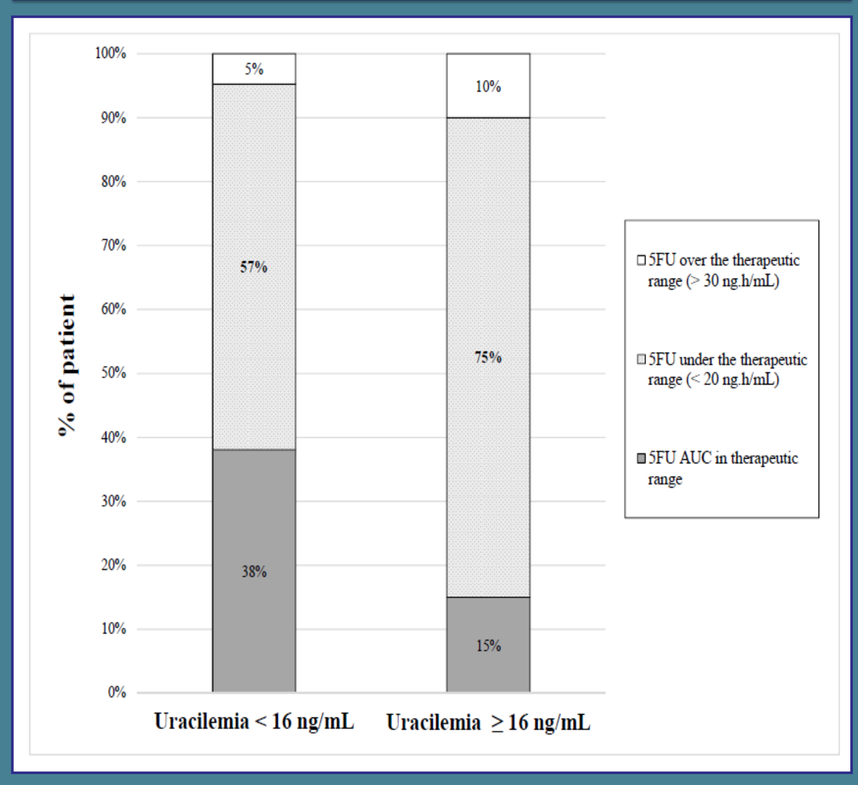
Age (years) (mean±SD)	66 ± 9.6
Sex	
M (n)	31
W (n)	11
Weight (kg) (mean±SD)	68.3 ± 14.5
5-FU protocol (n)	
carboplalin-5FU	3
FOLFIRI	1
FOLFIRINOX	10
FOLFOX	26
LV5FU2	1
DCF	1
DPYD Genotype	
No variant (n)	18
hapB3, c.1129-5923C>G (n)	2
5-FU dose at C1 (mg/m2) (mean (CV))	2094 (22%)
5-FU exposure (AUC in ng.h/mL) (mean (CV))	19.3 (43%)
Uracil	
Mean (ng/mL)	17.5
Min-max (ng/mL)	6-39.5
No DPD deficiency (%)	51
DPD deficiency (%))	49

Uracil plasma concentration does not predict 5FU exposure at C1

- No correlation between **uracil concentration** and **5-FU exposure at C1** (p = 0.6 (Pearson test))
- No correlation when 5FU AUC was normalized by the dose corrected by body surface area received at C1 (p = 0.15) (data not shown)



5FU underexposure was more frequent in patient with partial DPD deficiency than in patients without DPD deficiency



Discussion - Conclusion

- **DPD phenotyping is crucial** to identify patients with DPD deficiency leading to high risk of 5FU toxicity
- In patient with DPD deficiency, **it is challenging for clinicians to accurately determine the magnitude of the 5FU dose decrease** to apply at C1
- Pre-therapeutic DPD phenotyping (using uracilemia) **could not accurately predict 5FU exposure** at C1
- **Underexposure to 5FU is more frequent in patient with DPD deficiency**, likely due to a decrease of the first dose higher than necessary
- To optimize efficacy of 5FU-based anticancer therapy → **5FU therapeutic drug monitoring** should be systematically performed as a **complementary biomarker** to DPD phenotyping in **order to adapt 5FU dosages as soon as possible**.

References: [1]Goirand F. et al. How can we best monitor 5-FU administration to maximize benefit to risk ratio? Expert Opin Drug Metab Toxicol. (2018);14:1303-13.
[2]. Beumer JH. et al. Therapeutic Drug Monitoring in Oncology: International Association of Therapeutic Drug Monitoring and Clinical Toxicology Recommendations for 5-FluorouracilTherapy. Clin Pharmacol Ther. (2019);105:598-613.
[3]. My 5-FUTM, Saladax Biomedical (Bethlehem, USA)