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

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Introduction:
5-Fluorouracile (5FU) is a widely used cytotoxic agent. Dihyropyrimidine deshydrogenase activity deficiency (DPDd) detection by measuring plasma uracil is mandatory in France before treatment to identify at-risk patient of severe drug toxicity during the first administration. However, to date, no algorithm allows choosing the appropriate starting 5FU dose based on uracilemia. Therapeutic drug monitoring (TDM) of 5FU is recommended since 5FU exposure was shown to be associated with toxicity and efficacy of 5FU in several studies[1,2]. The aim of this work was to implement 5FU TDM to investigate the relationships between uracilemia, drug dosage and 5FU exposure at the first cure (C1) of chemotherapy.

Material and methods:
Patients treated for digestive cancer in Rennes regional anti-cancer center with a protocol including continuous infusion of 5FU were included from April to December 2019. Uracil was measured in plasma before treatment according to a validated HPLC-MS/MS method. Plasma 5FU, stabilized with DPD inhibitor, was quantified at steady state by immunoanalysis assay[3].

Results:
Thirty patients were included. No correlation was found between total dose/cure and 5FU exposure (AUC) (p=0.99). Sixty-two percent of patients received a lower dose of 5FU than the standard one at C1. Among them, 77% had uracilemia between 16-50 ng/mL (moderate DPDd). Sixty-eight percent of patients had 5FU exposure below the therapeutic threshold and 32% were within the recommended range. Underexposure was found in 57% and 83% of patients with normal and decreased DPD activity respectively.

Discussion / Conclusion:
This study confirms the high intra-patient variability of 5FU exposure. It shows that uracilemia could not accurately predict 5FU exposure since more than half of patients are underexposed regardless of their DPD phenotype. When empiric dose reduction is applied at C1 in case of partial DPDd, most patients are even more underexposed. Then, 5FU TDM implementation is feasible and appears of interest to optimized anticancer therapy.

Reference(s):
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.
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.
3. My 5-FUTM, Saladax Biomedical (Bethlehem, USA)

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