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Artificial increase of uracilemia during fluoropyrimidine treatment can lead to DPD deficiency misinterpretation

Each year in France, >75 000 patients receive fluoropyrimidines, including 5-fluorouracil (5-FU) and its oral prodrug capecitabine (Xeloda), to treat digestive, breast and head and neck cancers.[1] Among them, ∼20% will experience severe hematological and digestive toxicities and <2% will have a fatal outcome in the first two cycles.[1] A part of these toxicities may result from a deficiency in dihydropyrimidine dehydrogenase (DPD) which catabolizes the endogenous uracil (U) into dihydrouracil (UH_2) as well as 5-FU. In 2018, French Health Authorities [Haute Autorité de Santé (HAS) and Institut National du Cancer, (INCa)] recommended the evaluation of the enzymatic activity of DPD by measuring the plasma U concentration before administration of fluoropyrimidines.[2] To face the increased demand, a large number of both public and private laboratories have developed this assay. Although the recommendations state that blood samples should be strictly collected before treatment to assess the DPD basal activity,[2] clinicians might face situations in which sampling is performed during the 5-FU infusion or capecitabine intake. Thus an important but artificial increase of U—caused by competition with 5-FU for DPD-mediated metabolism[3,4]—might be misinterpreted by the clinicians as a profound DPD deficiency, leading them to reduce the dose inappropriately or, worse, stop fluoropyrimidines for patients who could have benefited from it.

In this context, we report 17 patients who were sampled on two occasions for DPD-deficiency testing, including one sample taken during 5-FU infusion (13/17, 76.5%) or close to the intake of capecitabine (4/17, 23.5%) and one outside any treatment period (baseline) (Table 1). Median delay between the two samples was 35 days (5-182 days). The mean percentages of variation of U, UH_2 and UH_2-to-U ratio compared with baseline reached +393%, +79% and −45%, respectively. The mean concentrations for U (11.7 *versus* 53.9 ng/ml) and UH_2-to-U ratio (13.1 *versus* 5.5) were statistically different between the two measurements ($P < 0.001$ and 0.015, respectively), whereas UH_2 was less affected (123.7 versus 178.4 ng/ml, $P = 0.127$).

Importantly, on the basis of the uracilemia threshold value of 16 ng/ml—established as the cut-off to attribute the status of partial deficiency[2]—we describe 12 patients (70.6%) wrongly classified as DPD deficient, whereas in reality their baseline uracilemia was indicative of a normal DPD status. Moreover, two patients (patient numbers 6 and 14) may have been misdiagnosed with a complete DPD deficiency (U > 150 ng/ml).

In conclusion, it is critical to remember the existence of this interaction between 5-FU and U occurring when sampling is performed during fluoropyrimidine exposure.

Table 1. Individual data of U, UH2 and UH2-to-U ratio values assessed during and out of the fluoropyrimidine treatment

Patient number	Fluoropyrimidine	U_0 (ng/ml)	U_1 (ng/ml)	Variation between P0 and P1 (%)	$UH2_0$ (ng/ml)	$UH2_1$ (ng/ml)	Variation between P0 and P1 (%)	$UH2/U_0$	$UH2/U_1$	Variation between P0 and P1 (%)
1	Capecitabine	9.7	**47.8**	+393						
2	5-FU	11.5	**26.9**	+134						
3	5-FU	11.2	**42.3**	+278						
4	5-FU	12.8	14.9	+16	150.8	279.8	+86	11.8	18.8	+59
5	5-FU	3.8	**32.8**	+763	77.2	241.7	+213	20.3	7.4	−64
6	5-FU	10.0	**157.0**	+1470	126.0	79.9	−37	12.6	0.5	−96
7	Capecitabine	12.0	**33.4**	+178	146.0	132.0	−10	12.2	4.0	−68
8	5-FU	**27.2**	**108.8**	+300	67.0	271.5	+305	2.5	2.5	+0
9	5-FU	6.1	11.0	+80	108.2	63.1	−42	17.7	5.7	−68
10	5-FU	12.8	**46.4**	+263	59.0	225.3	+282	4.6	4.9	+5
11	Capecitabine	**17.0**	**27.8**	+64	132.0	168.2	+27	7.8	6.0	−22
12	5-FU	4.0	**21.0**	+425	59.0	100.0	+69	14.8	4.8	−68
13	5-FU	8.0	**64.0**	+700	246.0	352.0	+43	30.8	5.5	−82
14	5-FU	**20.0**	**151.0**	+655	190.0	49.0	−74	9.5	0.3	−97
15	5-FU	11.8	**25.0**	+112						
16	5-FU	9.3	**71.9**	+673						
17	Capecitabine	12.3	**33.8**	+175						
Mean (standard deviation)		**11.7 (5.7)**	**53.9 (44.5)**	**+393**	**123.7 (58.9)**	**178.4 (101.7)**	**+79**	**13.1 (7.9)**	**5.5 (4.9)**	**−45**
P value[a]			0.0008			0.127			0.015	

U_0, $UH2_0$ and $UH2/U_0$: corresponding values to the basal activity of DPD, as sampling was performed out of fluoropyrimidine treatment (P0); U_1, $UH2_1$ and $UH2/U_1$: corresponding values when sampling was performed during fluoropyrimidine treatment (P1). Of note, not all laboratories assess UH2 concentration. Uracilemia values >16 and >150 ng/ml are shown in bold and are indicative of a partial or complete DPD deficiency, respectively.
U, uracil; UH2, dihydrouracil.
[a] According to the bilateral Student's paired *t*-test with *N*−1 degrees of freedom.

The subsequent risk of misinterpreting U values may lead to misclassify patients as DPD deficient. As information about treatment may not always be reported in the laboratory request for U, we recommend that laboratories systematically investigate for the presence of 5-FU in order to identify noncompliant samples. With this letter, we aim to alert and inform both clinical laboratories and physicians about the interpretation of these occasional, but challenging, situations to maximize the clinical benefits for patients scheduled to receive fluoropyrimidine-based chemotherapy.

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Novel drugs, familiar interactions: ciprofloxacin may increase exposure to the RET inhibitor pralsetinib

The Food and Drug Administration recently approved the oral tyrosine kinase inhibitor (TKI) pralsetinib as a novel treatment for REarranged during Transfection (RET) fusion-positive non-small-cell lung cancer (NSCLC). In the phase I/II study, the median objective response rate was 65% in treatment-naive and 61% in platinum-treated patients. The disease control rate was 93% and 95%, respectively.[1] Pralsetinib is under evaluation as a first-line strategy for RET-rearranged NSCLC.[2]

We report a case of a 60-year-old woman with metastatic RET-rearranged NSCLC who developed drug-related toxicity during concomitant consumption of ciprofloxacin and pralsetinib. The patient started full-dose pralsetinib 400 mg in the fourth-line setting on 14 August 2020 and did not report any major toxicity until October. She started empiric antibiotic therapy with ciprofloxacin 500 mg twice per day on 25 October due to fever.