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Fluoropyrimidine Dose Based on Uracil Plasma Concentration Impairs Survival in Patients

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Abstract

Fluoropyrimidine drugs (5-flurouracil (5-FU) / capecitabine) are the backbone of therapeutic regimens for digestive carcinomas and can lead to severe toxicities. To lower that risk, the French health authorities recommend dose adaptation based on plasma uracil concentration. Since dihydro pyrimidine dehydrogenase (DPD) catabolises more than 80% of 5-FU, a uracil threshold of ³16 ng/mL has been considered as partial DPD deficiency. 5-FU displays a dose-response relationship regarding both its efficacy and its toxicity we retrospectively assessed how this guideline has been applied in routine practice by evaluating fluoropyrimidine dosage and survival rate according to the 16 ng/mL uracil concentration threshold. Patients were included in this multicentre retrospective study if they had digestive cancer and a plasma uracil quantification performed between February 2018 and January 2020, and if they received at least one cycle of fluoropyrimidine-based chemotherapy in one of the four participating oncology departments. Among 302 patients included, 71 (23.5%) had a plasma uracil concentration ≥16 ng/mL. For the latter, the fluoropyrimidine was 0-50% of the theoretical dose in 60.5% of patients, 51-75% in 15.5%, and 76-100% in 24% at cycle 1 of treatment and the dose was increased after a well-tolerated first cycle for 7/69 (10.1%) patients at cycle 2 and for 13/69

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(18.8%) patients from baseline at cycle 4. Median time to failure was 8.6 months in those with uracil ³16 ng/mL and 24.3 months in the others; hazard ratio (HR) 0.38, 95% confidence interval (CI) [0.27; 0.53], p<0.0001. Overall survival was, respectively, 15.8 and 39.9 months; HR 0.46, 95%CI [0.29; 0.74], p=0.001). Tailored fluoropyrimidine dose impaired survival in patients with uracil ³16 ng/mL and we should consider to increase more frequently the fluoropyrimidine dose administered after a well-tolerated first cycle.

Keywords: Digestive carcinomas; Fluoropyrimidine dosage; Uracil; Toxicity; Predictive biomarker; 5-FU (5-fluorouracil).

Abbreviations: DPD: Dihydro Pyrimidine Dehydrogenase; EMA: European Medicines Agency; HPLC: High Performance Liquid Chromatography.

Introduction

Digestive carcinoma chemotherapy regimens are mostly based on fluoropyrimidine drugs (5-fluorouracil [5-FU] or capecitabine) [1-5]. However, 5-FU is mainly catabolised by dihydro pyrimidine dehydrogenase (DPD) [6], and partial or complete DPD activity deficiency can cause severe adverse reactions including death [7].

Different strategies have been proposed to predict DPD activity deficiency; the two main approaches are phenotyping the enzyme activity (directly or indirectly), or genotyping the four main polymorphisms of DPYD gene associated with 5-FU toxicity [8-12]. In February 2018, the French medicines agency (Agence nationale de sécuritédu médicament et des produits de santé) recommended DPYD genotyping for all patients receiving a fluoropyrimidine-based treatment to improve its safety as did later the European Medicines Agency (EMA) [13] and other pharmacogenetics working group. In contrast, the US Food and Drug Administration chose not to require any regulatory review of laboratory or genetic tests for use of 5-FU [14]. In December 2018 a new guideline from the French cancer institute (Institut National Du Cancer, InCA) and the French health authority (Haute Autorité de Santé, HAS) recommended the measurement of the plasma uracil concentration, and, based on a consensus, dose adaptation is required if this uracil level is between 16 and 150 ng/mL while another drug should be considered if it is greater than 150 ng/mL [15]. The aim was that phenotyping DPD activity could avoid severe adverse reactions due to unknown DPYD variants that impair DPD activity [16,17].

To our knowledge, no evaluation of this guideline in real-life practice has been reported, which is of importance since 5-FU displays a dose-response relationship regarding both its efficacy and its toxicity [18,19]. To address that matter, we conducted a retrospective study to evaluate how fluoropyrimidine dosage was adapted to uracil concentration and its impact on patient outcomes.

Materials and methods

Patients and study design

Patients were included in this multicentre retrospective study if they had digestive cancer and an plasma uracil quantification performed between February 2018 and January 2020, and if they received at least one cycle of fluoropyrimidine-based chemotherapy in one of the four participating oncology departments (Hôpital Edouard Heriot [Lyon], Centre Hospitalier de Lyon Sud [Lyon], Hôpital de la Croix Rousse [Lyon], Hôpital Nord-Ouest de Villefranche-sur-Saone [Gleize]). The objective was to compare time to failure (TTF) and Overall Survival (OS) among those with uracil <16 ng/ml to those with uracil ≥16 ng/ml. The following characteristics were collected from the patient medical files: histology, stage (localised vs metastatic disease), chemotherapy regimen, proportion of fluoropyrimidine dose administered, fluoropyrimidine induced-toxicity, date of progression and that of death (or last follow-up). The proportion of fluoropyrimidine dose administered and adverse reactions of fluoropyrimidine were assessed at cycle 1, 2 and 4 for those with uracil ³16 ng/mL to characterise early (1st and 2nd cycles) and long-term (4th cycle) dose adaptation. Last active search for vital status was March 30th 2021.

This is a non-interventional study and conducted according to the guidelines of the Declaration of Helsinki, and registered by the national data protection committee (Commission nationale de l'informatique et des libertés [CNIL] in March 2021, number 21_5368).

DPD phenotyping

Plasma uracil concentration was quantified by high performance liquid chromatography (HPLC) coupled with high resolution mass spectrometry detection [20]. The results were analysed by a senior biologist and the results of plasma uracil concentration were available to clinicians within 8 to 10 days from initial patient blood sample before the administration of treatment.

Statistical analysis

Data were described using median [interquartile range, IQR] and mean (standard deviation, SD) for continuous variables, and frequencies (percentage) for categorical variables. TTF and progression-free survival (PFS) was defined as the time from the first treatment with 5-FU / capecitabine to death or morphological progression according to RECIST criteria or clinical progression requiring a new anti-tumour treatment, whichever occurred first. PFS was used for metastatic disease only. OS was defined as the time from the first treatment with 5-FU / capecitabine to death or last follow-up. Patients without these events were censored at the time of last follow-up. TTF, PFS (for metastatic disease) and OS were estimated using the Kaplan-Meier method. Univariate analyses were performed using the Log-rank test for each variable of interest. Multivariate analyses using a Cox proportional hazards regression model were performed to identify factors independently associated with prognosis. All significant factors from the univariate analysis (Log-rank p<0.10) were included in the multivariate analyses; p<0.05 was considered statistically significant. The results from the survival analyses are presented with the effect estimates, hazard ratios (HR), and 95% confidence

interval (CI). All statistical analyses were performed using IBM-SPSS version 21.

Results

Patient characteristics

We identified a series of 334 patients with digestive cancers with a known plasma uracil concentration; 32 were excluded for missing data or lack of treatment with fluoropyrimidine (Figure 1).

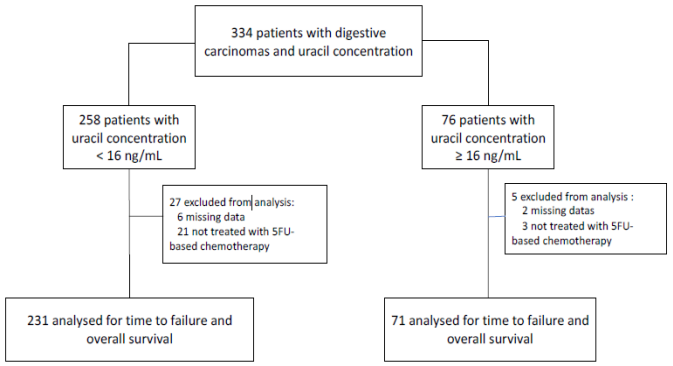

Figure 1: Study flow chart.

Patients with a plasma uracil concentration ≥16 ng/mL represented 23.5 % (71/302) of the total population. The two most frequent digestive cancers were colorectal adenocarcinoma and pancreatic adenocarcinoma; there was no significant difference between groups except for the prevalence of squamous cell carcinoma of oesophagus/anus (Table 1).

Fluoropyrimidine dose management of and toxicity evaluation

Among those with plasma uracil ³16 ng/mL, at cycle 1 continuous 5-FU or capecitabine dose was 0-50% of the theoretical dose in 60.5% of patients, 51-75% in 15.5%, and 76-100% in 24%; FU bolus was administered to 13.2% (9/68) of patients. Grade 3 or 4 fluoropyrimidine toxicity was observed in 2.8% of patients (2/71) after cycle 1 (Table 2). Fluoropyrimidine increased dose after a well-tolerated first cycle was observed for 7/69 (10.1%) patients at cycle 2 and for 13/69 (18.8%) patients at cycle 4. Among patients with plasma uracill <16 ng/mL, at cycle 1 the full dose of continuous 5-FU or capecitabine was administered to 97.4% of patients and 98.1% of patients received a 5-FU bolus. Grade 3 or 4 toxicity was experienced by 17 (7.4%) patients (Table 2).

Survival analysis

The median TTF was estimated to be 8.6 months among those with plasma uracil ³16 ng/mL, and 15.8 months among those with uracil <16 ng/mL; the risk of tumour progression was significantly higher among those with plasma uracil ³16 ng/mL (HR 0.38, 95%CI [0.27; 0.53], p< 0.0001). The median OS was estimated to be 24.3 months among those with plasma uracil ³16 ng/mL, and 39.9 months among those with uracil <16 ng/mL; the risk of death was significantly higher among those with uracil ³16 ng/mL (HR 0.46, 95%CI [0.29; 0.74], p=0.001; Figure 2).

Table 1: Patient characteristics according to plasma uracil concentration.

	Uracil >_16 ng/mL	Uracil <16 ng/mL	P value
Number of patients	71	231	
Median age (range)	70.3 (49.7-86.2)	67.5 (28-91)	
Male	44 (62%)	144 (62.3%)	0.96
Cancer type			
Colorectal ADK	29 (40.9%)	119 (51.5%)	0.11
Pancreatic ADK	20 (28.1%)	46 (19.9%)	0.14
SCC of oesophagus / anus	11 (15.5%)	10 (4.3%)	***0.001***
Gastric ADK	4 (5.6%)	31 (13.4%)	0.07
Neuroendocrine tumour	4 (5.6%)	15 (6.5%)	0.79
Other	3 (4.2%)	10 (4.3%)	0.97
Cancer stage			
Localised	25 (34.7%)	81 (35.1%)	0.96
Metastatic	47 (65.3%)	150 (64.9%)	0.96

ADK: Adenocarcinoma; **SCC:** Squamous cell carcinoma.

Table 2: Proportion of fluoropyrimidine dose administered and adverse reactions of fluoropyrimidine based on plasma uracil concentration.

	Uracil <16 ng/mL			Uracil 16 > ng/mL
	Cycle 1 (n=7)	Cycle 2 (n=67)	Cycle4 (n= 67)	Cycle 1 (n=231)
% of continuous 5-FU or Capecitabine, n(%)				
0-50%	43 (60.5)	36 (53.7)	36 (53.7)	2 (0.9)
51-75%	11 (15.5)	14 (20.4)	17 (25.4)	4 (1.7)
76-100%	17 (24)	17 (25.4)	14 (20.9)	225 (97.4)
Patients with a bolus of 5FU	9/68 (13.1)	9 (13.1)	7 (10.1)	207/211 (98.1)
G3 or G4 loxicity	2 (2.8)	0	0	17(7.4)
Patients with an increased dose after well-tolerated first cycle	-	7/69(10.1)	13/69 (18.8)	-

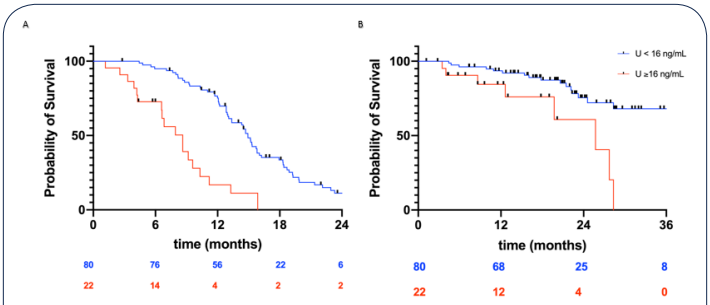

Figure 2: Kaplan-Meier curves of time to failure **(A)** and overall survival **(B)** according to plasma uracil concentration. The number of patients at risk are noted under each graph. Median TTF and median OS were estimated to be, respectively 8.6 and 24.3 months among those with uracil ³16 ng/mL and 15.8 and 39.9 months among those with uracil <16 ng/mL; the risk of failure and that of death was significantly higher among those with uracil ³16 ng/mL (PFS: HR 0.38, 95%CI [0.27; 0.53], p <0.0001; OS: HR 0.46, 95%CI [0.29-0.74], p=0.001).

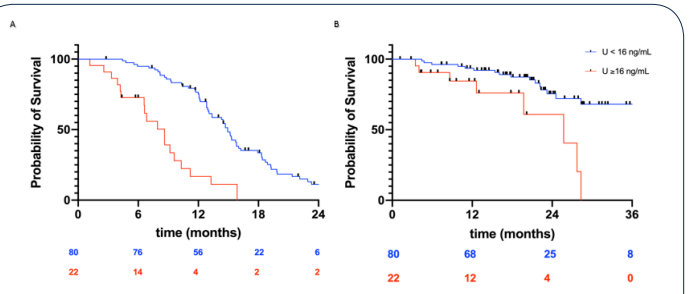

Figure 3: Kaplan-Meier curves of time to failure **(A)** and overall survival **(B)** according to plasma uracil concentration. The number of patients at risk are noted under each graph. Median TTF and median OS were estimated to be, respectively 8.6 and 24.3 months among those with uracil ³16 ng/mL and 15.8 and 39.9 months among those with uracil <16 ng/mL; the risk of failure and that of death was significantly higher among those with uracil ³16 ng/mL (PFS: HR 0.38, 95%CI [0.27; 0.53], p <0.0001; OS: HR 0.46, 95%CI [0.29-0.74], p=0.001).

For patients with metastatic colorectal adenocarcinoma, the median PFS and median OS were estimated to be, respectively 8.6 and 25.7 months among those with uracil ³16 ng/mL and 14.9 and 40.1 months among those with uracil <16 ng/mL; the risk of progression and that of death was significantly higher among those with uracil ³16 ng/mL (PFS: HR 0.26, 95%CI [0.11; 0.59], p <0.0001; OS: HR 0.29, 95%CI 0.09-0.97, p=0.02, 174 Figure 3).

In multivariate analysis, the factors significantly associated with TTF and OS were colorectal adenocarcinoma vs non-colorectal adenocarcinoma (HR for TTF 0.64, 95%CI [0.48; 0.86], p<0.003 and HR for OS 0.34, 95%CI [0.21; 0.54], p<0.0001), localised vs metastatic cancer (HR for TTF 0.25, 95%CI [0.17; 0.36], p<0.0001 and HR for OS 0.26, 95%IC A B[0.14; 0.48], p<0.0001) and full administrated fluoropyrimidine dose vs tailored (HR for TTF 0.14, 95%CI 0.06-0.34 and HR for OS 0.24, (95%IC [0.11; 0.55], p=0.001; Tables 3 & 4).

Table 3: Factors associated with time to failure (TTF).

	Univariate analysis			Multivariate analysis		
	Hazard ratio	**[95% CI]**	**P value**	**Hazard ratio**	**[95% CI]**	**P value**
Age, < *vs* ³ median	0.8	[0.60; 1.06]	0.13			
Sex, female *vs* male	0.92	[0.69; 1.23]	0.59			
colorectal adenocarcinoma vs Non-colorectal adenocarcinoma	0.72	[0.54; 0.96]	0.03	0.64	[0.48; 0.86]	0.003
Localised *vs* metastatic cancer	0.26	[0.18; 0.38]	<0.0001	0.25	[0.17; 0.36]	<0.0001
Fluoropyrimidine dose (full dose *vs* tailored*)	0.23	[0.17; 0.33]	<0.0001	0.14	[0.06; 0.34]	<0.0001
Plasma uracil concentration (<16 *vs* ³ 16)	0.38	[0.27; 0.53]	<0.0001	1.79	[0.74; 4.29]	0.193

Table 4: Factors associated with overall survival (OS).

	Univariate analysis			Multivariate analysis		
	Hazard ratio	**[95% CI]**	**P value**	**Hazard ratio**	**[95% CI]**	**P value**
Age, < *vs* ³ median	0.63	[0.41; 0.96]	0.03	0.53	[0.34; 0.82]	0.004
Sex, female *vs* male	0.88	[0.57; 1.38]	0.59			
Colorectal adenocarcinoma vs non-colorectal adenocarcinoma	0.38	[0.25; 0.60]	<0.0001	0.34	[0.21; 0.54]	<0.0001
Localised *vs* Metastatic cancer	0.29	[0.16; 0.54]	<0.0001	0.26	[0.14; 0.48]	<0.0001
Fluoropyrimidine dose (full dose *vs* tailored*)	0.28	[0.18; 0.45]	<0.0001	0.24	[0.11; 0.55]	0.001
Plasma uracil concentration (<16 *vs* ³ 16)	0.46	[0.29; 0.74]	0.001	1.66	[0.73; 3.76]	0.227

*<100% of continuous 5-FU or no bolus.

Discussion

In this retrospective cohort, we found that a tailored fluoropyrimidine dose impaired OS in patients with uracil ³16 ng/mL in routine practice. Univariate analysis found that those with uracil ³16 ng/mL and those with decreased fluoropyrimidine dose had a worse survival. As in multivariate analysis plasma uracil concentration was not associated to a worse prognosis, impaired survival in the plasma uracil ³16 ng/mL group was due to decreased chemotherapy dosage in this population. By applying the French recommendations in patients with uracil ³16 ng/mL, only 2.8 % of patients herein experienced G3 or G4 toxicity at cycle 1 but from baseline treatment dose was increased for only 18.8% of patients at cycle 4. The present study highlights that we should consider to increase more frequently the fluoropyrimidine dose administered after a well-tolerated first cycle. The results of the study also emphasise that plasma uracil is not a prognostic factor but that chemotherapy treatment displays a dose-effectiveness relationship as described in the literature [18]. However, many severe toxicities induced by fluoropyrimidine can be explained by partial DPD deficiency and complete DPD deficiency can lead to death [8,11,21]. To improve the identification of patients at high risk of toxicity, a combined composite biomarker should be proposed based on both phenotyping and genotyping of the DPYD gene. The latter is another way to evaluate DPD activity [22] and the reported experience of systematic genotyping DPYD gene in real-life practice indicated that the administration of 5-FU at reduced dose in patients heterozygous for DPYD*2A is safe [23]. The limitation of this technique is that in current clinical practice only four variants are tested for 5-FU toxicity (DPYD*2A, DPYD*13, D949V and HapB3), the use of which has failed to predict all cases of DPD deficiency – possibly because other genes are implicated in 5-FU toxicity and efficacy such as MTHFR, ABCB1 or TYMS [24,25,26]. Furthermore, to our knowledge, the impact of such testing in routine practice on survival has yet to be reported; only the impact on toxicity has been published [26,27]. The main limitation of the present study is its retrospective design that is associated with a risk of confusion bias. In addition, the participating centres are located in one administrative area of France, which may limit the generalizability of the results. In the future, a model that associates phenotyping DPD and genotyping DPYD with other genes of interest may be useful to better predict fluoropyrimidine toxicity and also to better adapt chemotherapy dosage.

Conclusions

The present study highlights that tailored fluoropyrimidine dose impaired survival in patients with uracil 16 ng/mL and we should consider to increase more frequently the fluoropyrimidine dose administered after a well-tolerated first cycle. These results should be confirmed by evaluating the clinical practice in the whole French territory.

Declarations

Funding: This research received no external funding.

Institutional review board statement: This is a non-interventional study and conducted according to the guidelines of the Declaration of Helsinki, and registered by the CNIL in March 2021, number 21_5368.

Informed consent statement: Informed consent was obtained from all subjects involved in the study.

Data availability statement: To protect patient confidentiality, the data will be consider for sharing only on written requests and on case-by-case basis.

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Conflicts of interest: The authors declare no conflict of interest.

Highlights

- Patients with uracil 16 ng/mL are treated with reduced doses of fluoropyrimidine
- Fluoropyrimidine dose is not always increased after a well-tolerated first cycle
- Patients with a reduced fluoropyrimidine dose have worse survival

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