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Ndiaye A

(1) Laboratory of Biochemistry and Molecular Biology, Faculty of Medicine, Pharmacy and Odontology, Cheikh Anta Diop University of Dakar, Senegal
(2) Laboratory of Biochemistry, Aristide Le Dantec Hospital, Senegal

Khole A

Laboratory of Biochemistry and Molecular Biology, Faculty of Medicine, Pharmacy and Odontology, Cheikh Anta Diop University of Dakar, Senegal

Samba A

(1) Laboratory of Biochemistry and Molecular Biology, Faculty of Medicine, Pharmacy and Odontology, Cheikh Anta Diop University of Dakar, Senegal
(2) Laboratory of Biology, Abass Ndao Hospital, Senegal

Thiam S

(1) Laboratory of Biochemistry and Molecular Biology, Faculty of Medicine, Pharmacy and Odontology, Cheikh Anta Diop University of Dakar, Senegal
(2) Laboratory of Biochemistry, Dalal Djam Hospital, Senegal

Soumah IY

Laboratory of Biochemistry and Molecular Biology, Faculty of Medicine, Pharmacy and Odontology, Cheikh Anta Diop University of Dakar, Senegal

Diedhiou F

Laboratory of Biochemistry and Molecular Biology, Faculty of Medicine, Pharmacy and Odontology, Cheikh Anta Diop University of Dakar, Senegal

Coly NF

UFR health of Thiès, Senegal

Cissé F

(1) Laboratory of Biochemistry and Molecular Biology, Faculty of Medicine, Pharmacy and Odontology, Cheikh Anta Diop University of Dakar, Senegal
(2) Laboratory of Biochemistry, Dalal Djam Hospital, Senegal

Diallo F

(1) Laboratory of Biochemistry and Molecular Biology, Faculty of Medicine, Pharmacy and Odontology, Cheikh Anta Diop University of Dakar, Senegal
(2) Laboratory of Biochemistry, Aristide Le Dantec Hospital, Senegal

Corresponding Author:**Ndiaye A**

(1) Laboratory of Biochemistry and Molecular Biology, Faculty of Medicine, Pharmacy and Odontology, Cheikh Anta Diop University of Dakar, Senegal
(2) Laboratory of Biochemistry, Aristide Le Dantec Hospital, Senegal

Dihydropyrimidine dehydrogenase (DPD) deficiency and side effects in cancer patients

Ndiaye A, Khole A, Samba A, Thiam S, Soumah IY, Diedhiou F, Coly NF, Cissé F and Diallo F

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Abstract

Introduction: Cancers are ranked among diseases with increasing prevalence and which treatment is based on cytotoxic products. The elimination of these products can be stopped by the deficiency of an enzyme which plays an important role in metabolism (DPD). This phenomenon can be the trigger of side effects. It is within this context that we decided to assay parameters (uracil, dihydrouracil) that allow us to evaluate the activity of DPD.

Methods: The study was carried out in patients with cancer. All clinical signs after chemotherapy were recorded. A blood sample was taken from these patients on EDTA tube and centrifuged at 4000 revolutions per minute for 8 minutes. Uracil (U) and Dihydrouracil (UH2) parameters were determined using the HPLC method after extraction.

Results: In our study population, we identified 29 patients who had not yet started chemotherapy whereas 74 had already started. Of those who started chemotherapy, 92% had side effects and only 8% were found without symptoms. In patients with U < 16 ng/ml, 45 had side effects while 20 did not. Patients with UH2/U > 13; 25 had adverse effects while 12 did not. Regarding DPD status among patients without DPD deficiency, 22 had adverse effects (21.4%) and 12 did not (11.7%).

Conclusion: The association between uracil concentrations and side effects showed that uracil levels above 150 ng/ml were consistently related to serious side effects, such as vomiting, diarrhea and general fatigue.

Keywords: Dihydropyrimidine dehydrogenase, cancer, toxicity

Introduction

Cancers are ranked among diseases with increasing prevalence every year. According to statistics, the number of cancer patients is projected to increase to 12 million by 2030 globally ^[1]. They are the cause of a large number of deaths with various risk factors and preventive and therapeutic strategies. Cancer treatment involves different approaches, including surgery, radiotherapy, cellular or monoclonal immunotherapy, oral targeted therapies, biotherapies and cytotoxic chemotherapy. These therapeutic strategies involve different protocols with different products.

Regarding chemotherapy, most protocols contain fluoropyrimidine-based products (5-fluorouracil), which are molecules with a narrow therapeutic index and many toxicities. They are not only used in metastatic situations, but also increasingly in adjuvant situations, i.e. for patients treated for a localized tumor at risk of relapse ^[2].

The metabolism of fluoropyrimidine products depends primarily on the activity of the dihydropyrimidine dehydrogenase (DPD) enzyme, involved in the degradation of natural pyrimidines. Indeed, it ensures the initial and limiting step of pyrimidine catabolism, thus involved in the degradation of chemotherapy drugs containing 5-FU or its analogues. Actually, more than 80% of the 5-FU administered is catabolized by DPD ^[3]. A deficiency of this enzyme can cause side effects in patients treated with these products. This study was conducted within that context to highlight the presence or absence of side effects in cancer patients undergoing fluoropyrimidine-based chemotherapy.

Methodology

A survey sheet was drafted to collect relevant data: This includes the patient's first and last name, date of last chemotherapy, products used, clinical signs noted after a chemotherapy

session...; for those who have already started their treatment.

In these patients, a blood sample was taken on EDTA tube and centrifuged at 4000 revolutions per minute for 8 minutes. Uracil (U) and Dihydrouracil (UH2) parameters were determined using the HPLC method after extraction. All results and epidemiological characteristics were reported using Excel 2016. The interpretation of the results was carried out with the following cut-off values:

Interpretation of uracil (U) concentration:

- $U < 16$ ng/mL: no DPD deficiency
- $16 < U < 150$ ng/mL: presence of partial DPD deficiency
- $U > 150$ ng/mL: presence of complete DPD deficiency
- Interpretation of the UH2/U report:
- $UH2/U > 13$: no DPD deficit
- $1 < UH2/U < 10$: presence of partial DPD deficiency
- $UH2/U < 1$: Presence of complete DPD deficiency

Results

In our study population, we identified 29 patients who had not yet started chemotherapy whereas 74 had already started. Of those who started chemotherapy, 92% had side effects and only 8% were found without symptoms.

Table 1: Distribution of patients with or without treatment

Patients	Actual	%
Not yet on chemotherapy	29	28
Under chemotherapy	74	72
-With symptoms	68	92
-Symptom-free	6	8

On average, the uracil concentration measured in patients was 17.44 ± 1.65 ng/ml. For dihydrouracil, the average measured in these patients was 177.95 ± 5.62 ng/ml. Regarding the ratio of dihydrouracil to uracil, we found an average of 12.6 ± 0.48 .

Table 2: Average of biological parameters

Parameters	Average
URACIL	17.44 ± 1.65 ng/ml
UH2	177.95 ± 5.62 ng/ml
UH2/U	12.6 ± 0.48

When it comes to uracil levels according to side effects, we found:

- For patients with $U < 16$ ng/ml, 45 had side effects while 20 did not.
- For patients with $U > 150$ ng/ml, only one patient experienced side effects.

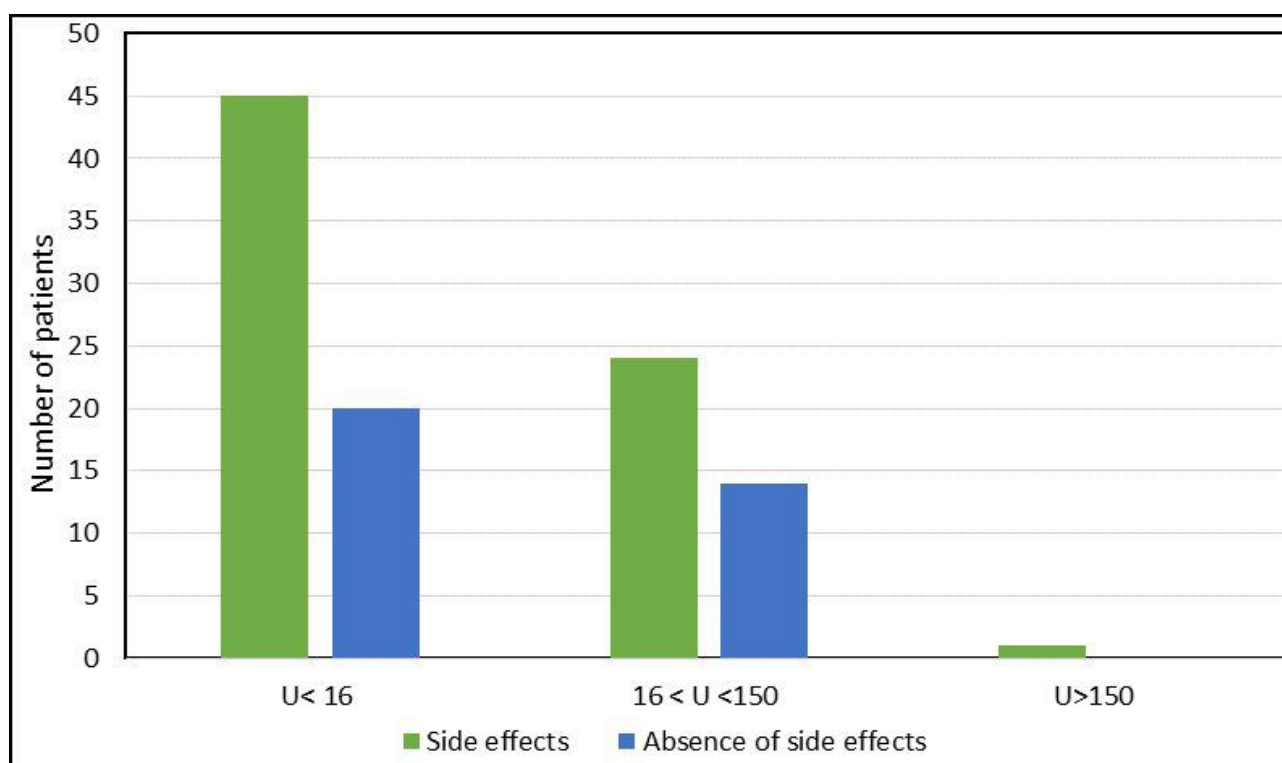


Fig 1: Association between the presence or absence of side effects and the level of uracil (U)

For the ratio of dihydrouracil to uracil:

- For patients with $UH2/U > 13$, 25 experienced side effects while 12 did not.
- For patients with $UH2/U < 1$, only one patient experienced side effects.

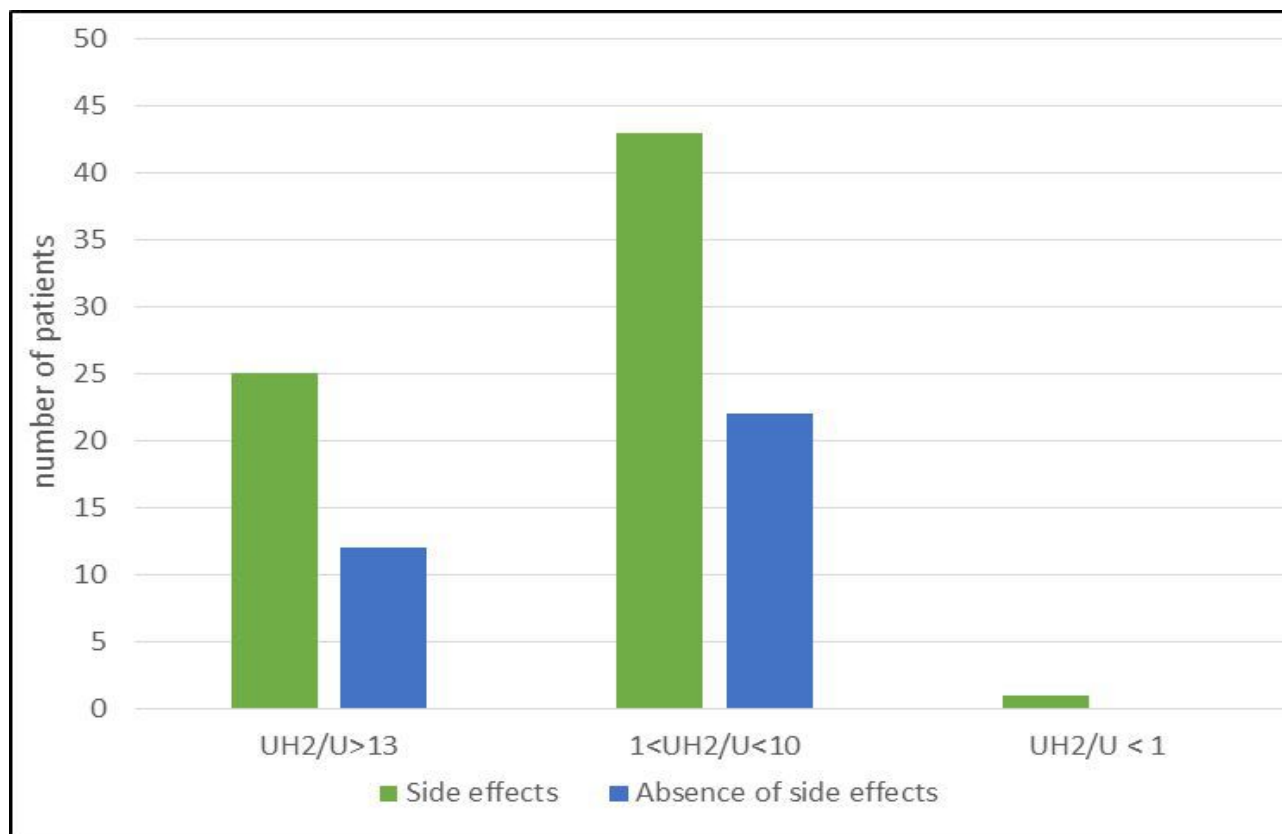


Fig 2: Association between the presence or absence of side effects and the UH2/U ratio

The DPO status shows that:

- Among patients without DPD deficiency, 22 experienced side effects (21.4%) and 12 did not (11.7%).
- Of those with partial DPD deficiency, 46 experienced adverse effects (44.7%) and 22 did not (21.3%).
- For patients with total DPD deficiency, only one patient experienced side effects.

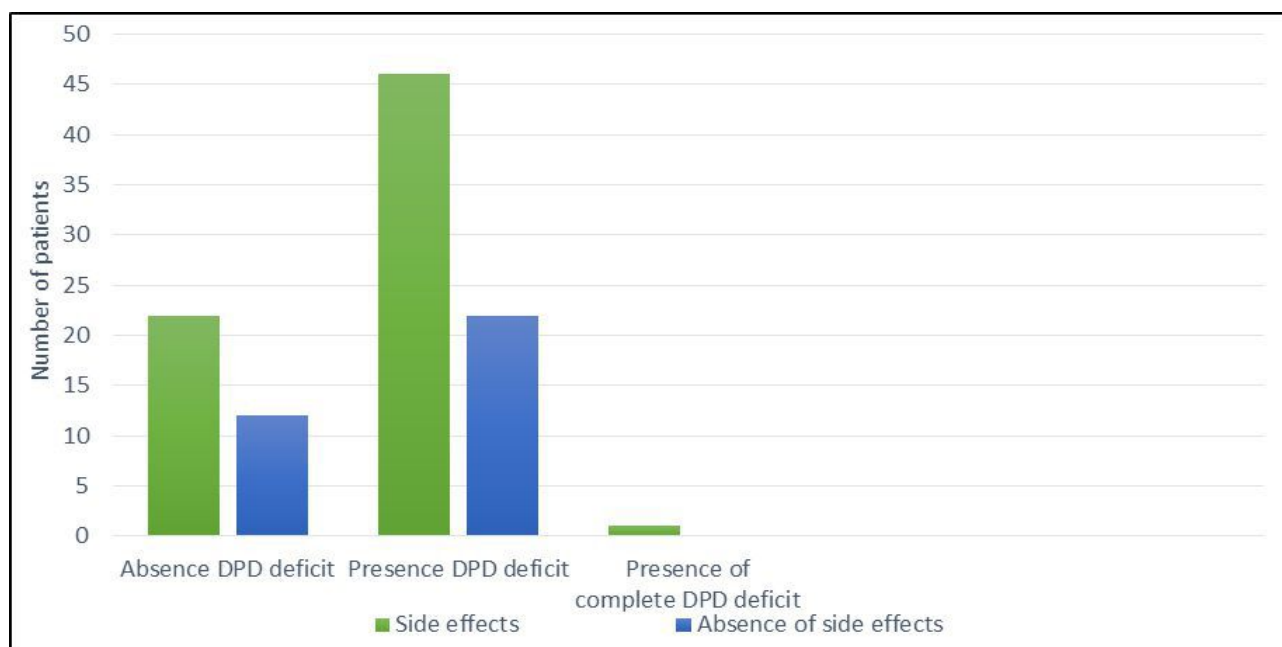


Fig 3: Association between absence or presence of adverse effects and DPD deficiency

Discussion

Dihydropyrimidine dehydrogenase (DPD) deficiency may cause toxicity in patients on fluoropyrimidine-based therapy. Studies have shown that this deficiency is the cause of many side effects in certain populations. To verify this relationship between the occurrence of these side effects and

DPD deficiency, we initiated this study on cancer patients, of whom 74 had already started chemotherapy with 5-fluorouracil.

In patients who have already started chemotherapy, we found that 92% developed symptoms after taking medication, and this has been illustrated by many studies.

For the UH2/U ratio in our study population, the mean value was 12.6 ± 0.48 with a standard deviation of 4.91 ± 0.95 . The lowest and highest values of this ratio were 0.2 and 28.1, respectively. Indeed, the mean uracil (U) was 17.44 ± 1.65 ng/ml with a standard deviation of 16.64 ± 3.23 ng/ml. The lowest and highest values for uracil were 5.8 ng/mL and 165.79 ng/mL. Compared to Caroline Calderon's results, the mean UH2/U in the patients was 10.70 ± 4.60 with the lowest value 0.74 and the highest value 24.61. For the same study, the mean uracil was 12.81 ± 7.81 ng/mL with the lowest value 3.87 ng/mL and the maximum value 62.38 /ml [4].

Among patients with uracil values below 16 ng/ml, 43.6% had side effects, in the following proportion:

- Vomiting in 17 patients (16.5%)
- Diarrhea in 12 patients (11.6%)
- Dizziness in 4 patients (3.8%)
- Fatigue in 12 patients (11.6%)
- Headache, general malaise, nausea, limb pain, body aches
- tremors, hot flashes, hair loss, dermatological problems

In this population, uracil $U < 16$ ng/ml was not significantly associated with the occurrence of side effects, as 19.4% of patients did not experience side effects.

For uracil values between 16 and 150 ng/ml, patients had side effects in the following proportion:

- Vomiting in 9 patients (8.7%)
- Diarrhea in 2 patients (1.9%)
- Dizziness in 3 patients (2.9%)
- Fatigue in 7 patients (6.8%)
- Pain on the left side of the heart, nausea, diarrhea, loss of saliva, loss of appetite, pain on the left side

We found a significant association with the occurrence of severe toxicities when uracilemia is ≥ 16 ng/ml. Indeed, the 2017 study on 550 patients by Meulendijks *et al.* [5] showed a clear correlation between uracil levels ≥ 16 ng/ml and early severe toxicity. In the same perspective, Boisdron-Celle *et al.* had similar results in 2006 [6]. In contrast to the studies by With *et al.* (2022) [7], their results showed a lack of a significant association between the occurrence of side effects and DPD status.

For uracil levels above 150 ng/ml, we found that 0.01% of patients had side effects such as general fatigue, chest pain, constipation, and lack of appetite.

These results can also be interpreted based on the UH2/U ratios which show that 25 patients experienced side effects when the UH2/U ratio > 13 , 43 with a ratio between 1 and 10 and one patient with a ratio of less than 1.

DPD status based on side effects reveals that 22 patients (21.4%) experienced side effects in the absence of DPD deficiency, 46 patients (44.7%) with partial deficiency and 1 patient (0.9%) with complete deficiency. According to the Hagiwara study, DPD deficiency was noted in the presence of many grade 3 side effects during the first cycle of chemotherapy in a 64-year-old patient [8]. These results have been confirmed by several authors, all corroborating the fact that the incidence of level III, IV or V side effects is higher in patients with partial DPD deficiency [9, 10].

Conclusion

The association between uracil concentrations and side effects showed that uracil levels above 150 ng/ml were

consistently associated with serious side effects, such as vomiting, diarrhea and general fatigue. Similarly, a UH2/U ratio greater than 13 was also correlated with an increase in symptoms, thus corroborating the use of this ratio as an indicator of toxicity.

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