Original Research

5-fluorouracil therapeutic drug monitoring and adverse events in a Romanian population

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Abstract

Fluoropyrimidines represent the backbone of many chemotherapy protocols and the standard treatment for many types of tumors. Toxicity associated with fluoropyrimidines can occur in up to 40% of cases.

Background and purpose. The objective of this study was to analyze the correlation between the plasma concentration of 5-fluorouracil and the adverse events that patients might experience during this therapy.

Methods. A total of 58 patients received 5-fluorouracil-based chemotherapy. A blood sample was collected from each patient during the drug infusion, in order to assess the area under the curve for 5-fluorouracil. The occurring adverse events were evaluated through medical recordings of the patients' reported symptoms, clinical and paraclinical examinations.

Results. In our study, the majority of patients experienced some type of toxicity. Moreover, we found a correlation between 5-FU plasma concentration (expressed as AUC) and adverse events, a stronger one with hematological adverse reactions and a weaker one with gastrointestinal and cardiovascular toxicity.

Conclusion. Determining the plasma concentration of 5-FU in patients with severe toxicities could represent a method of individualizing the treatment and improving the safety profile.

Keywords: fluoropyrimidine, therapeutic drug monitoring, adverse events

Background and aim

Fluoropyrimidines represent the backbone of various chemotherapy regimens, and they are used in many types of tumors, such as head and neck, breast, esophageal, gastric, biliary, colorectal, and anal cancer [1]. The fluoropyrimidines used in clinical practice are 5-fluorouracil (5-FU), Capecitabine (Cap), Tegafur, S-1 (tegafur/gimeracil/oteracil), and TAS-102 (trifluridine/tipiracil).

5-FU administration has evolved from bolus intravenous to continuous intravenous infusion, hybrid bolus and continuous intravenous infusion regimens, alone or in combination with other agents, and with the addition of folinic acid for modulating and potentiating its actions [1].

The most common adverse events (AEs) are represented by bone marrow suppression, diarrhea, emesis, mucositis, fatigue and hand-foot syndrome. The intravenous bolus administration is responsible for hematologic AEs, while continuous intravenous infusion for gastrointestinal AEs. The most severe and sometimes even life-threatening AEs are represented by cardiotoxicity, ranging from chest pain to myocardial infarction and sudden death [2]. Fluoropyrimidines can cause severe toxicity in up to 40% of patients and deaths in 0.2% to 0.8% [3].

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Several factors are associated with 5-FU treatment-related toxicity, such as the dosage, type, duration of administration, biomodulation by folinic acid, co-medication, comorbidities, age, and genetic factors such as variants of the 5-FU-metabolising enzymes [4].

Monitoring 5-FU plasma concentration serves as a method for individualization of 5-FU dose. Optimization of 5-FU pharmacokinetics in models has been complicated for bolus i.v. administration. Still, in case of intermittent and continuous administration, plasma levels increase until a steady plateau is reached [5]. The infusion pump speed variability influences the steady-state plasma concentration of 5-FU [6]. The pharmacokinetic parameter most strongly associated with a biological effect is the total drug exposure or the area under the curve (AUC) of the drug concentration [7]. Determination of AUC for bolus 5-FU schedules is challenging due to the short time span when samples must be collected [7]. Determination of AUC levels in patients receiving 5-FU in continuous infusion regimens is more straightforward because only one sample is needed, which is usually collected at a steady state, at any time after the first 2 hours of infusion and throughout the infusion, until the end [7]. 5-FU AUC can be calculated based on the steady-state drug concentration measurement (Css), constant during continuous infusion and the pump infusion time [8]. A known relationship exists between 5-FU plasma concentration and the biological effects, including toxicity [9].

Several studies have found that an optimal anti-tumor 5-FU effect with minor toxicity and side effects is achieved when AUC ranges between 20-30 mg*h/L [10]. However, when 5-FU AUC is lower than 20 mg*h/L, the anti-tumor therapy is not effective enough; therefore, increasing the 5-FU dose may be necessary [10,11]. When AUC is greater than 30 mg*h/L, the patient has an increased risk of developing severe adverse events, therefore reducing the dose may be necessary [10,11].

The purpose of our study was to assess the plasma 5-FU concentration, calculate the AUC and its correlation with the adverse events in a Romanian population, and see if we can use this parameter to individualize our patients' treatment.

Methods

Clinical data

This was a prospective observational study which took place within "Ion Chiricuță" Institute of Oncology of Cluj-Napoca, Romania, between April 2019 and March 2022. The study received favorable approval to be carried out both from the Ethics Committee of the Iuliu Hatieganu University of Medicine and Pharmacy Cluj-Napoca and from the Ethics Committee of the "Ion Chiricuță" Institute of Oncology of Cluj-Napoca. Data such as gender, age, tumor location, tumor stage, chemotherapy regimen, drug dosage, comorbidities, and adverse events were collected from the hospital electronic database. The patients were monitored during at least four treatment cycles.

The inclusion criteria were the following: (1) patients with the indication of 5-FU treatment in monotherapy or combination regimens, regardless of the treatment setting, neoadjuvant/adjuvant or palliative, (2) patients older than 18 years, and (3) patients who signed informed consent to be enrolled in the study. The main exclusion criteria were (1) patients with incomplete medical records, (2) patients with important comorbidities such as NYHA IV heart failure, symptomatic ischemic heart disease, previous myocardial infarction, severe renal chronic disease, severe hepatic failure, and severe respiratory failure, (3) patients who discontinued treatment of their own will.

The purpose of this study was explained to each patient, and after they agreed to be part of it, they all signed an informed consent. All the patients' data were anonymized. Participation in this study was voluntary, the European ethical recommendations regarding the absolute confidentiality of personal data collected in the study was complied with, as well as with the anonymity and safety of the participants (Regulation (EU) 2016/679 on the protection of natural persons regarding the processing of personal data and regarding the free circulation of this data). The participants were informed that they would not benefit materially from being included in this study. A written informed consent was obtained from all patients.

Sample collection and extraction

The chemical substances and reagents used in our study were standard 5-fluorouracil (5-FU), 5-bromouracil (5-BC), HPLC grade acetonitrile, and ammonium acetate.

The blood from the patients was collected 12 hours after the start of the continuous infusion, through a venepuncture different from the infusion port, as this could have led to false results, even if the port was washed several times before collection. Plasma was obtained by centrifugation at 2500 x *g*, 4ºC for 20 min. The separated plasma was kept at -80°C until extraction, and was divided into aliquots of 0.6 ml in 1.5 ml Eppendorf tubes. Plasma samples were quantified using the method described by Amasya et al [12]. Accordingly, a Waters Alliance 2695 HPLC-UV system equipped with a quaternary pump, degasser and autosampler were used. The HPLC apparatus was coupled with a UV/Visible detector (2489 Waters). Chromatographic separation was performed using an Hilic HPLC column (Luna ® 5 µm Hilic 200 Å; 150 x 4.6 mm, Phenomenex) at 40°C. The chromatographic separation was done using the isocratic elution of acetonitrile: 5 mM ammonium acetate, 95:5 (v/v) solution (pH 7, adjusted with 1 M NaOH). The absorbance was measured at 265 nm. The flow rate was of 1 ml/min, while the injection volume was of 10 µl. The autosampler temperature was set at 4°C. Empower software was used for data acquisition and analysis. The identification of 5-FU was made according to the UV−visible spectra, co-chromatography with standard retention time, and literature data. The quantity was expressed as ng/ml 5-FU equivalents.

Five mg of 5-FU standard and 5 mg of 5-BC internal standard were accurately weighed and dissolved in 5 ml each, in order to obtain a stock solution of 1 mg/ ml, respectively. The stock solution was diluted with acetonitrile to obtain a concentration range between 0.33 and 340 µg/ml for both compounds. The dilutions were freshly prepared each day using HPLC vials. Before injecting into the HPLC system, the solutions were filtered using 0.45 µm nylon filters. An aliquot of 250 µl of each plasma sample was loaded into 30 mg/1ml Strata™ XA 33 mm polymeric strong anion tubes (Phenomenex). The tubes were fixed on a complete extraction unit (LiChrolut, Merck, Darmstadt, Germany). The cartridges were prior conditioned with 1 ml of methanol and equilibrated with 1 ml of water. Afterwards, samples were loaded and washed with 1 ml of 25 mm ammonium acetate and 1 ml of methanol for plasma protein removal. The interest compounds were eluted using 1 ml of formic acid: methanol solution (5:95, v/v). After elution, the solution was injected into the chromatograph system.

Assessment of adverse events

The Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, published on November 27, 2017, was used as evaluation criteria for AEs [13]. We analyzed the presence of hematologic, gastrointestinal, cardiovascular, and cutaneous AEs. Hematologic AEs quantified were anaemia, leukopenia, neutropenia, and thrombocytopenia.

Statistics

We used Microsoft Excel in order to create a database that contained the clinical data, as well as the AUC calculation and the unidimensional analysis. For the two-dimensional data analysis, we used the SPSS Modeler 17.1 software, through which we performed the Chi-square test and determined the Pearson association coefficient.

Results

Patient and tumor characteristics

This study included 58 patients who received 5-FU-based chemotherapy regimens. Male patients represented 71% of study population. The average age of both genders was 59.18 years, 27 patients were under 60 years of age, whereas 31 were over 60 years of age (Table I). The performance status was 1 in 72.4% of the cases. The treatment was palliative in 37.90% of the patients (Figure 1). The distribution of patients by tumor location was 22 patients with head and neck squamous cell cancer, 35 with gastrointestinal tumors, and one with penile cancer (Figure 2).

Disease stage was established according to the American Joint Committee on Cancer (AJCC) 8th edition. 63.8% (n=37) of the patients had a stage IV disease, patients with stage III represented 31% (n=18) of all patients, and stage II – 5.2% (n=3) (Figure 3). 44 patients did not present any associated medical conditions. Among those who presented associated diseases, type 2 diabetes mellitus, arterial hypertension, benign prostatic hypertrophy, chronic alcoholism, smoking, chronic obstructive broncho pneumopathy, and asthma were listed. We stratified patients with other associated pathologies based on how many diseases they had (Figure 4). None of the associated medical conditions of the patients represented an exclusion criterion from the study.

Table I. Demographic data of study patients.

	% (n)
Sex	
Male	71 (41)
Female	29 (17)
Age	
Average±SD	59.18±8.7
<60 years	46.55 (27)
≥60 years	53.45 (31)
Performance status	
0	19 (11)
1	72.4 (42)
2	8.6 (5)

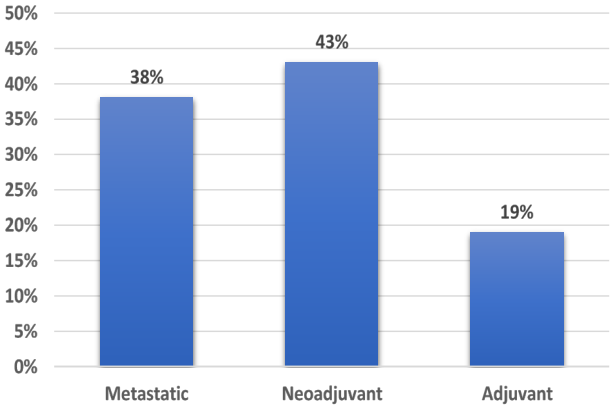

Figure 1. Distribution of patients based on treatment setting.

Chemotherapy regimens

The choice of the chemotherapy regimen was made according to the existing guidelines on each tumor site. Regarding the 5-FU-based regimens, 21 patients received TPF, two patients PF4, five FLOT, four FOLFIRINOX, and 26 FOLFOX4 (Figure 5).

The 5-FU-based regimens description is the following: a) FOLFIRINOX 5-FU bolus iv 400 mg/mp, continuous infusion 1200 mg/mp (day 1, day 2 – pump for 23 hours/day); b) FOLFOX4 5-FU bolus iv 400 mg/mp, continuous infusion 600 mg/mp (day 1, day 2 – pump for 22 hours/day); c) FLOT 5-FU continuous infusion 2600 mg/mp (day 1 – pump for 24 hours/day); d) TPF 5-FU continuous infusion 1000 mg/mp (day 1- 4 – pump for 24 hours/day); e) PF4 5-FU continuous infusion 1000 mg/mp (day 1 – 4 – pump for 24 hours/day).

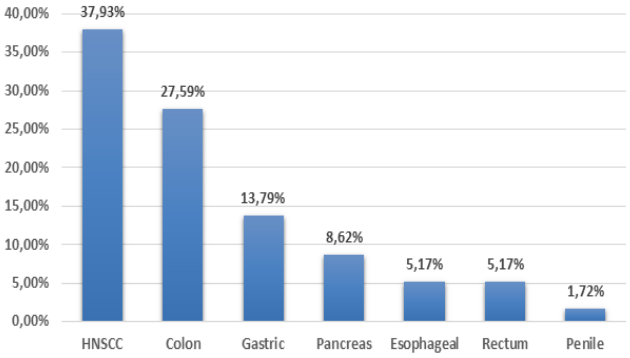

Figure 2. Distribution of patients based on tumor site.

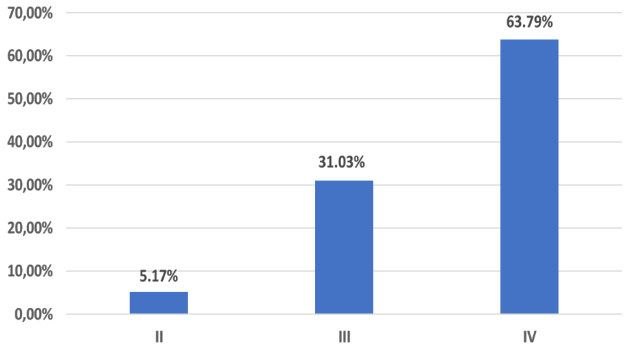

Figure 3. Distribution of patients based on tumor stage.

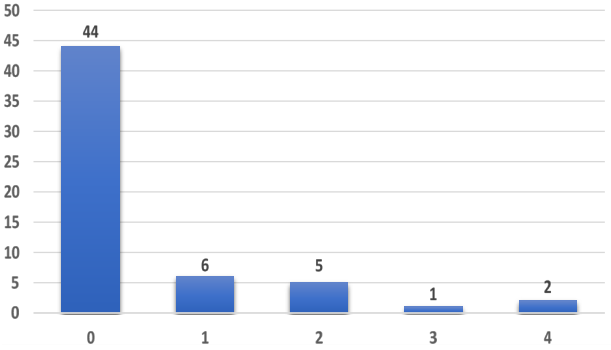

Figure 4. Distribution of patients based on associated conditions.

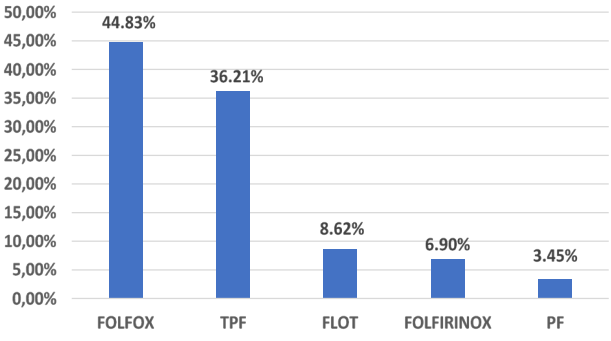

Figure 5. Distribution of patients based on 5-FU-based regimen.

The pharmacokinetic analyses were performed after we obtained the 5-FU plasma concentration at a steady-state, and we calculated the AUC. For AUC calculation, we used the following formula: AUC (mg*h/l) = 5-FU plasma concentration (ng/ml) x pump maintenance time (h)/1000. The target range for efficiency and a good safety profile of AUC based on data from previous studies was of 20-30 mg*h/l. 5-FU exposure varied among patients, ranging between 11.93-55.41 mg*h/l. More than half of the patients had an AUC <20 mg*h/l, 24 patients between 20-30 mg*h/l, and four patients of >30 mg*h/l (Figure 6).

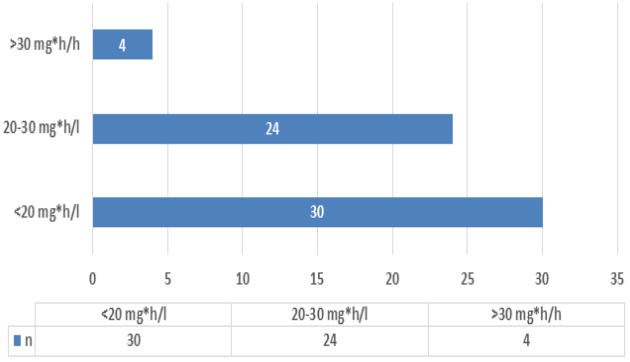

Figure 6. Distribution of patients based on 5-FU AUC.

The incidence of AEs was significant. 93% (n=54) of patients experienced an AE of any grade. Patients experienced a single type of AE, or they experienced associated AEs. The most frequent were hematological AEs with an incidence of 84.48% (Table II). Almost 35% of patients had AEs ≥ grade 3, and approximately 58.5% had AEs ≤ grade 2 (Table III). None of the patients had a grade V adverse event.

Table II. Incidence of adverse events.

Type of toxicity	N	%
All adverse events	54	93.1
Hematological AE	49	84.48
Cardiac AE	5	8.62
Gastrointestinal AE	23	39.66
Skin AE	2	3.45

Table III. Distribution of patients based on adverse events grade.

Toxicity grading	N	%
0	4	6.90
I	19	32.76
II	15	25.86
III	10	17.24
IV	10	17.24
V	0	0

Almost half of the patients with hematological toxicity (n=24) had grade I AE, followed by grade II in 24.49% and grade IV in 18.27% (Figure 7). Of the nine cases of grade IV AEs, six presented febrile neutropenia that required hospital admission and the administration of antibiotic treatment according to clinical protocols.

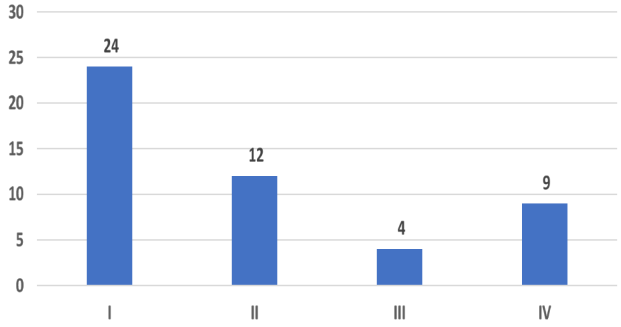

Figure 7. Distribution of patients based on the grade of hematological toxicity.

Of all the patients with hematological toxicity, 22 presented toxicity of a single hematopoietic cell line, 15 on two hematopoietic cell lines, and 12 on all three (Figure 8).

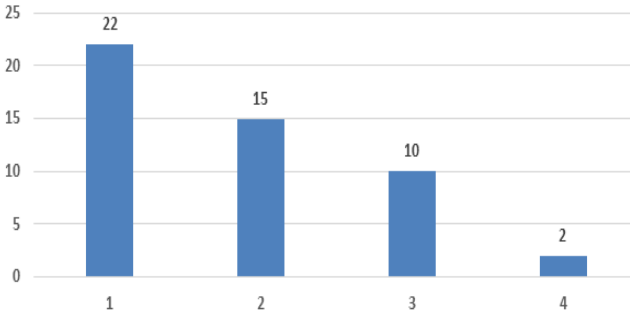

Figure 8. Distribution of patients with hematological AEs.

Regarding the patients with gastrointestinal AEs, grade III was the most frequent, in 43.48% of the patients, followed by grade II in 30.43% and grade I in 26.05%. of the patients. None of the patients had a life-threatening AE (Figure 9). Gastrointestinal toxicity symptoms reported by the patients were nausea with or without vomiting, diarrhea, or oral mucositis. Among the patients who experienced grade III toxicity, the majority had more than seven watery stools per day and hospital admission was necessary.

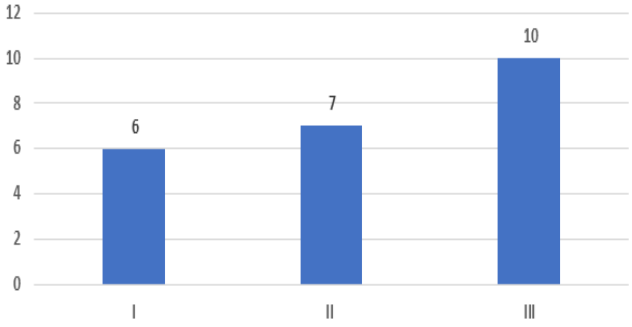

Figure 9. Distribution of patients based on the grade of gastrointestinal toxicity.

Two patients experienced skin AEs. One patient had grade II skin toxicity manifested by hyperkeratosis, cracks on the palms and soles, skin scaling, whereas the second case presented grade III toxicity, additionally associating pain to the previous manifestations. Five patients presented clinical, biological, and electrocardiographic manifestations of cardiovascular toxicity. Out of those five patients, one had a myocardial infarction during the 5-FU continuous infusion, and four had grade II toxicity manifested either by moderate chest pain, or asymptomatic, and with minimal elevation of the cardiac enzymes, non-specific electrocardiographic changes inconsistent with myocardial infarction (Figure 10).

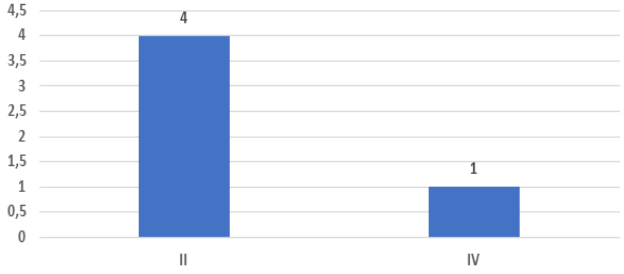

Figure 10. Distribution of patients based on the grade of cardiovascular toxicity.

The aim of the study was to assess whether the concentration of 5-FU expressed through AUC correlates with the presence of adverse reactions. We analyzed 5-FU AUC and hematological AEs and determined the Pearson correlation coefficient, which has a value of 0.305, meaning that there is an association of medium intensity between the two variables. There is also a weak correlation between gastrointestinal and cardiovascular adverse events and 5-FU AUC, with a correlation coefficient of 0.083 and 0.036, respectively. There was only a small number of patients with skin toxicity, therefore it was not relevant in order to determine the Pearson coefficient.

The correlations between AUC and age, as well as between AUC and the number of comorbidities are both of weak intensity, with a Pearson coefficient of -0.03, and -0.22. There was no correlation between patients' gender and AUC.

Discussion

Several studies have associated the 5-FU plasma levels with toxicity, but also with efficacy, and demonstrated that both correlations could be improved by dose adjustment [6]. The therapeutic drug monitoring (TDM) of 5-FU plasma concentration aims to personalize the treatment with increased effectiveness and an acceptable safety profile.

However, 5-FU TDM is currently hampered by the following challenges: (1) 5-FU is rapidly catabolized after blood collection by the DPD enzyme, which is present in blood cells. Therefore, rapid centrifugation or the immediate addition of a stabilizing agent, a DPD inhibitor, is required; (2) improper sample preservation can produce falsely low 5-FU concentration measurements, which could lead to overdosing of the patient in the following cycle; (3) the inaccuracy of running time of infusion pumps for 5-FU; for example, the elastomeric pump is sensitive to pressure, temperature, patient's activity and season and the portable pump delivers several boluses [14-18].

In our study, due to the lack of a DPD inhibitor, we needed to centrifuge the samples collected from the patient within the shortest possible period of time, the sample had to arrive at the laboratory within a maximum of one hour after collection. The administration of 5-FU according to the protocols that required continuous infusion for several hours was carried out using elastomeric pumps. Both situations could alter the results of the plasma concentration of 5-FU.

Collecting patients' data in the study was difficult because of the need for more information from the physical and electronic files of the patients. The follow-up in order to monitor the effectiveness of the treatment could not be carried out properly either because the patients performed the imaging assessments in other clinical units, or because many patients opted for switching treatment administration at the territorial hospitals, especially during the restrictions caused by the COVID-19 pandemic.

One of the significant limitations of our study was the small number of patients. There were several patients who met the criteria for inclusion in the study, but did not want to be included. Another factor that made it difficult to include patients in the study was the COVID19 pandemic, which affected the addressability of patients, especially during the restrictions period. But, despite this, we were able to establish the existence of a medium-intensity correlation between 5-FU AUC and hematological adverse events, as well as a very weak intensity correlation between 5-FU AUC and cardiovascular and gastrointestinal adverse reactions. Because of the small group of patients, we could not highlight an association between AUC values above the established target range and the severity of the adverse events.

Starting with March 2020, EMA recommends testing DPD deficiency in each patient before treatment with a fluoropyrimidine (EMA), and this can be done by measuring uracil levels or by checking for the presence of specific mutations of DPYD [19,20]. Two guidelines can help clinicians in the decision to adjust doses depending on DPYD genotyping, namely the Clinical Pharmacogenetics Implementation Consortium guideline (CPIC) and the Dutch Pharmacogenetics Working Group guideline [19,20]. Both guidelines offer beneficial recommendations, but neither includes 5-FU TDM.

Swiss Groups of Pharmacogenomics and Personalized Therapy recommend 5-FU TDM in patients with a DPYD variant and in whom starting doses are reduced based on this genotype in order to minimize the risk of underdosing [1]. In Romania, DPYD gene mutation testing is not reimbursed, so only a few patients undergo this testing. Also, none of the phenotypic methods to assess DPD deficiency recommended by EMA and other European guidelines are currently performed in Romania. In the daily clinical practice, in case of a higher than grade III AE, according to CTCAE, oncologists in Romania usually decrease the dose by 25%, or recommend testing the DPYD gene mutation. But, given the extremely low incidence of the mutation, many cases with severe toxicities cannot be currently explained. By determining the plasma concentration, we could thus adjust the dose in patients with severe toxicity, without affecting the efficacy.

The measuring of the 5-FU concentration in our study was performed within a doctoral research project, the routine determination not being available to any oncologist because of the lack of HPLC equipment in hospital laboratories.

Conclusion

Although there is a large number of new anti-cancer therapies currently available, chemotherapy, namely fluoropyrimidines in this case, remains the standard treatment in many tumors, either alone or in combination with targeted therapy or immunotherapy. Toxicity of fluoropyridines is an important concern that might lead to dose reductions and loss of effectiveness, to treatment discontinuation or to patient's hospital admission and even death. A better understanding of the time and reasons of occurrence, and of the best measures to be taken in case of severe toxicity could help in reducing risks for the patients and provide treatment for longer periods of time.

As far as we know, our study is the first study on a Romanian population that seeks to show a correlation

between the plasma concentration of 5-FU and the adverse events associated with this treatment. Despite the limitations of this study, determining the plasma concentration can be an important tool to guide the treatment of patients with severe adverse events that require the reduction of treatment doses, without decreasing effectiveness.

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