Original Research

Therapeutic drug monitoring as a tool to optimize 5-FU−based chemotherapy in gastrointestinal cancer patients older than 75 years

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Abstract *Aims:* Most clinical trials exclude elderly people, leading to a limited understanding of the benefit-to-risk ratio in this population. Despite existing data regarding the oncological management of elderly receiving fluorouracil (5-FU)-based regimen, our objective was to investigate 5-FU exposure/toxicity relationship in patients ≥75 years and compare the effectiveness of 5-FU therapeutic drug monitoring between elderly and younger patients.
Methods: Hundred fifty-four patients (31 of whom are older than 75 years) with gastrointestinal cancers, who were to receive 5-FU−based regimens, were included in our study. At cycle 1 (C1), the 5-FU dose was calculated using patient's body surface area, then a blood sample was drawn to measure 5-FU concentration and 5-FU dose was adjusted at the subsequent cycles based on C1 concentration. Assessments of toxicity were performed at the beginning of every cycle.
Results: Seventy-one percent of elderly patients required dose adjustments after C1, compared with 50% for younger patients. Percentages of patients within 5-FU area under the curve range at cycle 2 were 64% and 68%, respectively, for elderly and younger patients. The proportion of elderly patients experiencing severe toxicities fell from 15% at C1 to only 5% at cycle 3.

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Conclusion: Pharmacokinetic-guided 5-FU—dosing algorithm, leading to an improved tolerability while remaining within therapeutic concentration range, is even more valuable for patients older than 75 years than in younger patients.

1. Background

Since its original synthesis in the late 1950s, fluorouracil (5-FU) continues to be widely used in the treatment of many cancers, including oesophagus, stomach, pancreas and colorectal cancer (CRC) both as adjuvant therapy of early stage or in advanced setting [1,2]. Over the last decades, knowledge improvement in 5-FU pharmacokinetics (PK) and mechanism of action led to development of new treatments, based on the addition of the biomodulating agent folinic acid, association with other cytotoxic drugs, or modification of 5-FU administration schedule. Originally, 5-FU alone was delivered as a bolus. Nowadays, administration by continuous intravenous (i.v.) infusion is used. Indeed, it was shown that this delivery method increased 5-FU exposure duration, leading to an improved cytotoxic activity and clinical effectiveness, while limiting toxicity [3—5]. Despite these therapeutic progresses, 5-FU is often the source of severe treatment-related toxicities requiring hospitalisation and leading to death in 0.5%—2% of cases [6—8].

The most well-known biochemical cause of intolerance to fluoropyrimidines is deficiency of dihydropyrimidine dehydrogenase (DPD) [9,10]. DPD is defined as the first and rate-limiting enzyme in the catabolic pathway of 5-FU, responsible for more than 80% of 5-FU elimination [11,12]. Partial or complete deficiency in the DPD enzyme has been observed in 3—5% and 0.1% of the general population, respectively [13—15]. DPD-deficient patients experience excessive and severe toxicity in the form of neutropenia, diarrhoea, mucositis and hand—foot syndrome. Overall, DPD deficiency is observed in 39—61% of patients developing severe toxicity [8,16]. In all patients, DPD deficiency is confirmed by sequence analysis of *DPYD*, the gene encoding DPD, used as predictor of fluoropyrimidine-related toxicity when a pathological mutation is found. To date, more than 30 sequence variations in the DPD gene have been identified, with the most well-established variant being *DYPD*2A* [17,18]. To improve efficacy and reduce toxicity, previous investigations focused on the relationship between 5-FU plasma concentration and DPD activity to determine individual dose adjustment in patients presenting DPD gene mutation [19—22]. However, 5-FU PK variability is affected by many others factors such as sex, disease status, nutritional condition, organ function and comedication,

explaining frequent overexposure and underexposure despite 5-FU dosage adjustment by *DYPD* genotype.

5-FU dosing is traditionally calculated as per the body surface area (BSA). Recent data confirm the lack of scientific rational for 5-FU BSA-based dosing [23]. As previously demonstrated, there is no potential correlation between BSA and 5-FU plasma clearance [24], possibly explaining the large 5-FU interindividual concentrations variation in patients treated with standard schedule based on BSA. Because 5-FU is characterised by a strong toxicity—exposure relationship and a narrow therapeutic window, the use of therapeutic drug monitoring (TDM) approaches are greatly supported [25,26]. Some studies have demonstrated successful strategies to monitor 5-FU blood concentrations and adjust individual doses based on systemic exposure [27—30]. Area under the curve (AUC) of 5-FU concentrations is considered to be the most relevant PK parameter associated to 5-FU—related efficacy and toxicity. Because of its intrinsic variability, it is generally considered that an AUC range of 20—30 mg h/L is required for successful therapy [31,32]. In our centre, we have chosen to use an algorithm based on Gamelin's study [29]. Owing to the precision of 5-FU measurements, a small dose modification (i.e., ±5%) would not have a clinical or biological incidence; we extended the Gamelin's range of target AUC to 18—28 mg h/L, to start dose adjustment at ±10%.

Currently, 60% of malignant disease occurs in persons older than 65 years, and more than half of these patients are older than 70 years. However, most clinical trials exclude elderly people by design. Consequently, limited data are available to explore the risks and benefits of specific cancer-treatment regimens in this population. Commonly, chemotherapy doses are empirically reduced in elderly patients, mainly to prevent serious side effects. In therapeutic trials and randomised studies, 5-FU adjuvant monotherapy has shown comparable benefits and similar toxicity rates for patients 65 years and older as for younger one's [33,34]. Nevertheless, this knowledge is based on clinical trials which, by definition, select patients less likely to have comorbidities or functional impairments when compared with the general elderly population.

To date, no initial 5-FU dose reduction is recommended for elderly patients, but in clinical practice, empirical dose reductions or shorter chemotherapy

Table 1
Initial patients characteristics and treatment regimens.

Variable	Young (n = 123)	Elderly (n = 31)	P-value
Gender, n (%)			
Male	69 (56.1)	20 (64.5)	NS
Female	54 (43.9)	11 (35.5)	NS
Age (years) median (range)	64 (27—74)	79 (75—87)	**< 0.001**
Weight (kg) mean ± SD (range)	69.5 ± 15.1 (35—115)	70.9 ± 13.3 (47—109)	NS
Height (cm) mean ± SD (range)	168.9 ± 8.4 (150—186)	166.4 ± 8.2 (150—182)	NS
Charlson Comorbidity Index, median (range)	/	10 (5—13)	/
Location of cancer, n (%)			
Colorectal	70 (56.9)	23 (74.0)	NS
Pancreas	31 (25.2)	2 (6.5)	**0.026**
Oesophagus	9 (7.3)	2 (6.5)	NS
Stomach	8 (6.5)	2 (6.5)	NS
Others	5 (4.1)	2 (6.5)	NS
Type of chemotherapy, n (%)			
Metastatic	105 (85.4)	23 (74.2)	NS
Adjuvant	18 (14.6)	8 (25.8)	NS
Protocol of chemotherapy, n (%)			
Simplified FOLFOX-6	44 (35.8)	17 (54.8)	NS
FOLFIRINOX	47 (38.2)	3 (9.7)	**0.002**
FOLFIRI	22 (17.9)	6 (19.4)	NS
LV5FU2	4 (3.3)	4 (12.9)	NS
FOLFIRI-3	6 (4.8)	1 (3.2)	NS
Biotherapy, n (%)			
Yes	59 (48.0)	15 (48.4)	NS
No	64 (52.0)	16 (51.6)	NS
Line of treatment, n (%)			
1st line	58 (47.2)	21 (67.7)	**0.043**
2nd line	39 (31.7)	6 (19.4)	NS
3rd line or more	26 (21.1)	4 (12.9)	NS

SD, standard deviation; NS, non-significant; FOLFOX, oxaliplatin, folinate, 5-FU; FOLFIRINOX, irinotecan, oxaliplatin, folinate, 5-FU; FOLFIRI, irinotecan, folinate, 5-FU; LV5FU2, folinate, 5-FU.

regimens are often prescribed in elderly patients because of the hypothetical risk of toxicity. Thus, the main objective of the present study is to investigate exposure/toxicity relationship of 5-FU—based regimens in individuals aged ≥ 75 years. The secondary objective of this work is to compare the effectiveness of 5-FU TDM between elderly and younger patients.

2. Patients and methods

2.1. Population

This retrospective analysis was carried out in a database covering all patients diagnosed with gastrointestinal cancer who received a 46-h continuous 5-FU infusion from April 2014 to February 2016 in the Dijon's Cancer Centre (Burgundy, France). The therapeutic follow-up in our centre includes a blood sample analysis to determine 5-FU exposure during the three first chemotherapy cycles. Patients eligible for this study were treated with specific digestive cancer treatment regimens by 5-FU infusion alone or associated with other cytotoxic ± biotherapy for adjuvant or advanced therapy purposes. The data routinely collected include gender, age, birth date, weight, height, Charlson Comorbidity Index (CCI) (elderly only), primary tumour, type of treatment (metastatic or adjuvant), treatment line, chemotherapy regimen, date of cycle, 5-FU bolus dose, 5-FU infusion dose, 5-FU concentration measured, AUC calculated, proposed dose for the next cycle and toxicities. Individuals were classified into two groups based on age: young group rounded up patients <75 years and elderly included all patients ≥ 75 years.

2.2. Study design and chemotherapy regimen adjustment

At cycle 1 (C1), patients received folinic acid (400 mg/m²) by i.v. infusion over 2 h followed by a 5-FU bolus (400 mg/m²) and immediately after by 46-h continuous 5-FU infusion (2400 mg/m²) administered via a battery-operated pump. Patients could receive other cytotoxic drugs and/or biotherapy before 5-FU regimen. AUC of 5-FU infusion was calculated by multiplying the 5-FU steady-state concentration by the infusion duration (46 h). At the cycle 2 (C2), the dose of 5-FU infusion was determined as per an algorithm derived from Gamelin's one, targeting AUC range of 18—28 mg h/L. The same methodology was applied at C2 to ensure correct exposure and perform dose adaptation at the cycle 3 (C3) if necessary. Doses were to remain constant during the subsequent cycles, except in case of severe toxicity. Clinicians were free

to individually adapt any other drug doses included in the protocol.

2.3. Blood sampling and plasma concentration determination

To limit within-day variability of DPD activity [35], blood samples were taken between 8 and 10 a.m. the day after the beginning of 5-FU infusion. Samples were immediately centrifuged, and plasma was kept frozen at −20 °C until analysed. Plasma 5-FU concentrations were determined by liquid chromatography. Chlorouracil was used as internal standard. 5-FU was extracted from the plasma with isopropanol−ethyl acetate (15/85 v:v) in the presence of 200 mg ammonium sulphate to precipitate proteins. The organic phase was dried at 50 °C under nitrogen dioxide and reconstituted with 200 μL of mobile phase before injection. The mobile phase consisted of methanol/water (5/95 v:v). UV detection was performed at 265 nm. This method was fully validated for routine measurement of 5-FU with a lower limit of quantification of 30 μg/L.

2.4. Toxicities classification

All toxicities were graded according to the Common Terminology Criteria for Adverse Events (version 4.0) and were clinically or biologically evaluated before each cycle with particular attention to diarrhoea, neutropenia, mucositis and hand−foot syndrome. Severe toxicity was defined as grade III or grade IV toxicity.

2.5. Statistical methods

The distribution of patients' characteristics was expressed as percentages or mean values presented as mean ± SD (range) or median (range) if deemed appropriate. The statistical analysis was conducted in patients older than 75 years or younger than 75 years. Univariate analyses were performed. Quantitative data were analysed using Student's test or non-parametric Mann−Whitney test for small sample size (effective < 30). Percentages were compared using two proportions comparison test, Pearson's Chi-squared test for multiple samples or Fisher's exact test for small sample size. The level of statistical significance was set at $p = 0.05$. Most analyses were performed using SIGMAPLOT$^{©}$ software (version 11.0; SYSTAT Software, Inc).

3. Results

3.1. Patient characteristics

A total of 154 patients with gastrointestinal cancer were enrolled in our study. Thirty-one of them were older than 75 years and were included in the elderly group, whereas 123 were included in the younger adult group.

Demographic data and study treatment details are listed in Table 1.

The most frequent cancer which affects each group was the CRC (74% in elderly and 56.9% in younger adult). Pancreas was the second most frequent site (25.2%) in young adults, whereas there was as much pancreatic cancer as stomach or oesophagus cancer (6.5%) in the elderly. The proportion of patients treated in adjuvant and in metastatic settings was similar in both groups. However, when only FOLFIRINOX regimens were considered, there were significantly more treated patients (38.2%) in younger adults than in elderly (9.7%). Overall, elderly patients received 28.2% less irinotecan-based chemotherapy than younger patients. It should be noted that 67.7% of elderly were treated as first-line therapy.

3.2. Interindividual variability in 5-FU PK

Fig. 1 represents plasma 5-FU concentrations as a function of 5-FU-infusion dose (calculated as per the BSA) for each patient at C1. No proportionality between dose and concentration was found. A considerable difference in blood concentrations was observed for a same 5-FU dose in both groups. For example, in elderly, steady-state 5-FU concentrations were ranging from 110 μg/L to 706 μg/L for an identical total dose of 4000 mg. Similar conclusions could be drawn from younger patients, but this variability seems to be much more substantial among elderly. Consequently, the goal of 5-FU BSA dosing (i.e., bring all patients in the same target exposure) is not reached, and those results confirm the need to use another dose adjustment
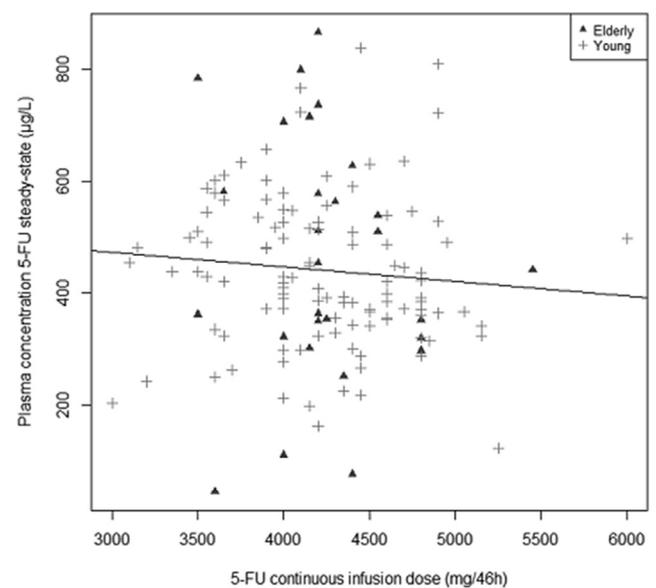

Fig. 1. Relationship between 5-FU plasma concentration and 5-FU continuous infusion dose at cycle 1 in elderly and young patients. 5-FU, fluorouracil.

method than calculating 5-FU dose as per the BSA and more for elderly patients.

To confirm that 75 years old was a valuable cut-off, proportions of patients inside or outside the 5-FU AUC range were compared for four age ranges (Table 2). AUC distribution was not significantly different between the three youngest groups (p = 0.920). To note, there was no patient overexposed in the group of 55 years or less. On the contrary, the proportion of patients ≥75 years well exposed did not reach 30% (i.e., 24% less compared with 65−75 years group (p = 0.039)). Applying a cut-off value of 70 years would lead to no significant difference in terms of proportion of patient well exposed between 65 and 70 years (50%) and 70 years or more (40%) groups (p = 0.386). Same results were observed for underexposed patients (36% vs 42%, p = 0.583) and overexposed patients (14% vs 18%, p = 0.611). Thus, a cut-off value of 75 years was considered as pertinent.

3.3. Impact of 5-FU TDM and individual dose adjustment to reach target AUC range

At C1 (i.e., with dose adapted as per the BSA), the mean initial exposure for elderly patients was 21.2 ± 10.1 mg h/L and 20.2 ± 6.2 mg h/L for younger adults with a 47% and 30% coefficient of variation (%CV) in each of the groups. Mean doses administered to elderly (4239 ± 418 mg) were not significantly different from the ones administered to younger adults (4234 ± 536 mg) (p = 0.951), which might explain why no difference was found between AUC in the two groups (p = 0.598). However, when AUC %CV are compared between C1 and C3 (i.e. after 2 cycles of TDM), an important decrease (−20%) is observed for elderly. This decrease reflected a lesser AUC variability among individuals.

As shown in Fig. 2, at C1, where the initial 5-FU infusion doses were calculated based on BSA, only 29% of elderly presented an AUC within the therapeutic range, whereas 50% of younger adults were within this same range (p = 0.049). Of the 13 elderly patients who were underdosed at C1, 11 of them (85%) had a dose adjustment at C2 with an average increase of 963 mg (23%) compared with the mean initial dose of 5-FU. Interestingly, after 5-FU PK-guided dosing adjustment, the percentage of elderly patients below the target AUC decreased from 46% (13 of 28) to 25% (7 of 28) between C1 and C2, whereas the percentage of elderly within the

Table 2
Percentage of patients with 5-FU AUC values below, within and above the therapeutic range by age groups.

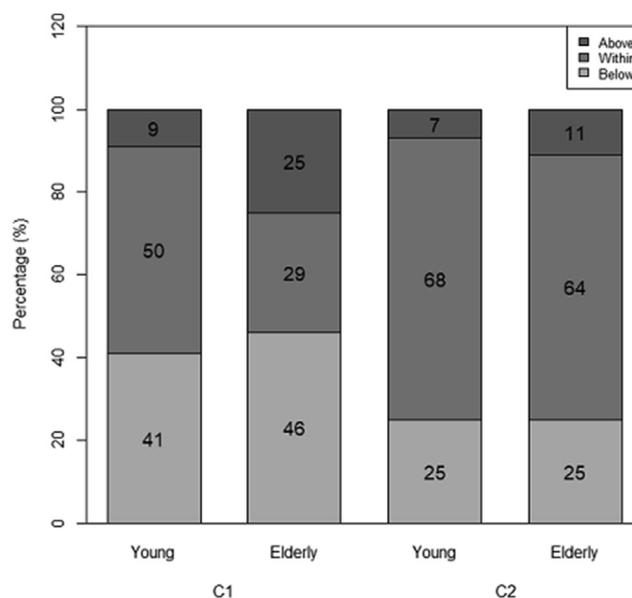| AUC range	<55 yr	55−65 yr	65−75 yr	≥75 yr
Below (%)	53	39	36	46
Within (%)	47	51	53	29
Above (%)	0	10	11	25

AUC, area under the curve.

Fig. 2. Percentage of patients with 5-FU AUC values below, within or above the therapeutic range at C1 and C2. AUC, area under the curve; 5-FU, fluorouracil.

therapeutic range significantly increased from 29% (8 of 28) at C1 to 64% (18 of 28) at C2 (p = 0.011). Similarly, the proportion of younger patients who had an AUC within the therapeutic range progressed from 50% to 68% between the two first cycles (p = 0.008). At C2 and C3, there was no statistically significant difference concerning proportion of underexposed, well-exposed or overexposed patients in both groups.

3.4. Relation between 5-FU exposure and toxicity

Main adverse events in the two groups were analysed at C1. Adverse events such as diarrhoea, hand−foot syndrome and neutropenia tend to be more frequent in the younger group than in the elderly group; however, differences were not statistically significant. The incidence of severe mucositis (grade ≥ III) was relatively low in both groups, but elderly patients tended to be more exposed than younger patients (7.1% vs 2.7%, respectively, p = 0.024).

At C1, 10% of elderly below or within AUC range declared severe toxicity compared with 29% of those above AUC target. The only grade III/IV toxicity, below or within therapeutic AUC range, declared among elderly patients was mucositis. Elderly patients above the AUC range presented mostly neutropenia and diarrhoea. The incidence of serious toxicities for patients below or within AUC range did not differ significantly between the two groups (p = 0.905), as for patients above AUC range (p = 0.683).

All cycles combined, lower AUC values were observed for elderly presenting no toxicity or at least non-severe (grade I/II) (21.3 ± 7.7 mg h/L) compared with those presenting severe toxicity (grade III/IV) (28.2 ± 7.7 mg h/
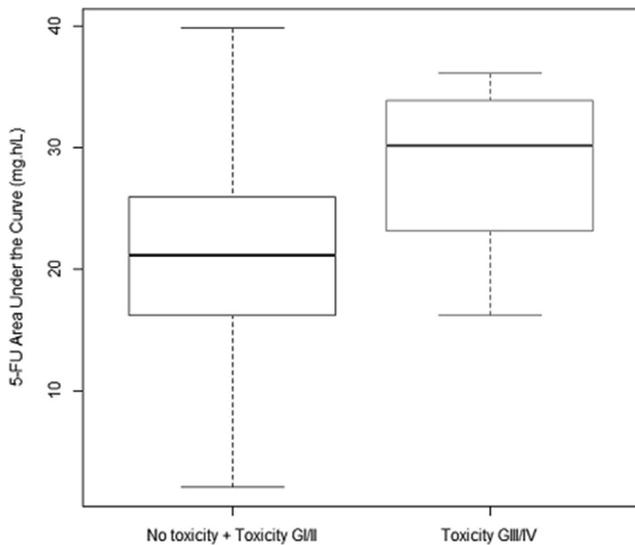
Fig. 3. Distribution of elderly patients presenting no toxicity or at least non-severe compared with those presenting severe toxicity according to AUC values. AUC, area under the curve; 5-FU, fluorouracil.

L) (Fig. 3). Conversely, all cycles and grade combined, patients overdosed presented almost twice as much toxicities than patients underdosed or well dosed (67.3% vs 35.8% respectively, p < 0.0001).

3.5. Impact of 5-FU PK-guided dosing adjustment to reduce toxicity

At C1 and C3, lower incidence of grade III/IV toxic effects was observed for both groups (Fig. 4). Decrease of severe toxicities was even more important for elderly (15% vs 5% respectively). were with grade I Of note, no
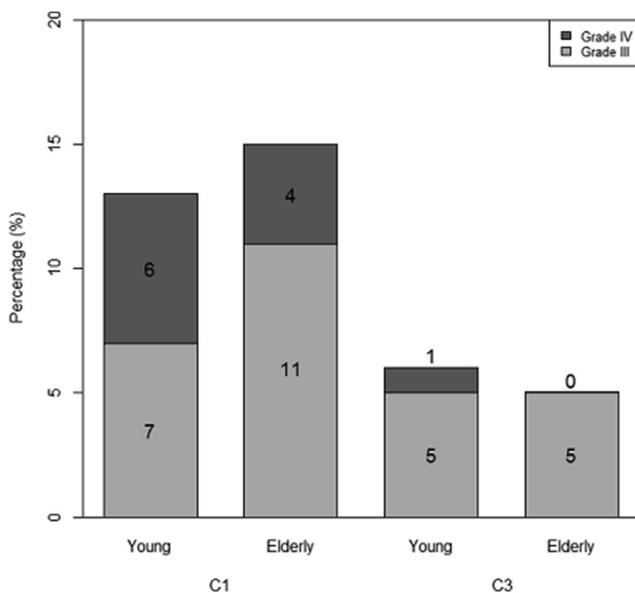

Fig. 4. Percentage of elderly and young patients developing severe adverse events at C1 and C3.

grade IV toxicities at cycles 2 and 3 were observed in the elderly group when compared to one patient with a grade IV toxicity at cycle 1.

Seven young patients benefited from 5-FU bolus dose reduction between C1 and C2, due to grade IV toxicities or hospitalisation during the intercycle period. Among them, four patients had also a 5-FU infusion reduction, whereas only 1 of them was overexposed. Three elderly patients had bolus dose reduction due to grade III adverse events (N = 2) and/or overexposure (N = 2). The two patients who had AUC above target benefited from an infusion dose reduction as well. Overall, all cycles combined, 3 of 5 elderly and 5 of 13 young patients presented toxicities despite the absence of 5-FU bolus dose (mostly grade I/II for the 2 groups) and in the absence of an overexposure for most of them.

3.6. Relationship between CCI and PK or toxicity

Comorbidity was calculated for all elderly patients; CCI ranged from 5 to 13, with 28 patients having a CCI $\geq$ 6. All cycles combined, no correlation between comorbidity score and 5-FU AUC value was observed (r^2 = 0.0204). Similarly, the median of CCI was not statistically different between the no toxicity and at least non-severe group compared with the severe toxicity one (p = 0.057).

4. Discussion

Considering population ageing and the increasing proportion of elderly patients treated for cancer in general and particularly for gastrointestinal cancer, it is important to evaluate the impact of cytotoxic agents, such as 5-FU, in this population. Such studies could have a major impact in the improvement of elderly patient management in current practice. Indeed, ageing can alter physiological functions and biological characteristics which could change the PK of drugs, modify the plasma concentrations, and, consequently, affect the tolerability and effectiveness of the chemotherapy. Even if Etienne's PK analysis [36] revealed that age, as model covariate, had a negative impact on 5-FU clearance, other publications founded no significant influence of age on liver DPD activity [37—39]. Furthermore, Duffour's article [40], which compared 5-FU PK parameters between two groups (age < or $\geq$ 65 years) receiving LV5FU2 regimen, indicated that mean clearance in elderly patients did not differ from younger people. Because no initial 5-FU dose reduction is recommended for patients with altered renal or hepatic function, elderly patients should be treated as younger patients. However, in current clinical practice, empirical dose reductions or shorter chemotherapy regimens are often prescribed in elderly patients, mainly due to fear of severe toxicity.

Although 5-FU dosing is traditionally calculated as per the BSA, a number of studies have been conducted to evaluate an appropriate dose adjustment algorithm and to demonstrate the advantage of 5-FU PK-guided dosing to reduce toxicity and enhance therapeutic outcomes. Nevertheless, those studies mainly concerned young patients (<65 years old), and very few data exist for elderly ones. In our study, we have chosen to divide our population by age range and evaluate 5-FU AUC range for each group to find optimal cut-off value of age. Our data suggest that 75 years as a cut-off is better than the more frequently used 65 or 70 years. Indeed, we demonstrated that 5-FU BSA dosing in 75 years or older patients is even less suitable than in young people (only 29% of well-expose with dose adapted as per the BSA), leading to a non-optimal treatment in this frail population. In this article, we show that 5-FU PK-guided dosing may help to reduce toxicity from C1 to subsequent cycle in elderly patients and while increasing the dose in underdosed patients.

At the first cycle, mean 5-FU doses administered to elderly (4239 ± 418 mg) were not different from those administered to young people (4234 ± 536 mg). However, a difference in terms of 5-FU combination was observed. Indeed, elderly received nearly 30% less irinotecan-based chemotherapy (the cornerstone of first-line metastatic CRC) than younger patients, whereas 48% of them received a first-line metastatic chemotherapy. This observation suggests that oncologists, in our cancer centre, tend to favour less aggressive regimens more than 5-FU dose reduction in elderly patients.

As a reminder, for this study, individual doses adjustment was based on systemic exposure measured at the previous cycle. A range of 18–28 mg h/L, based on Gamelin's algorithm [29], was used as the target AUC. Upon BSA-based dosing at C1, only 29% of the older than 75 years group had a 5-FU AUC within the target range, whereas 50% of young patients were within this therapeutic range. This result leads to an important variability in 5-FU steady-state concentrations, ranging, for example, from 110 µg/L to 706 µg/L for an identical total dose of 4000 mg for elderly. In comparison, PK-guided 5-FU dosing performed at C2 resulted in significantly higher proportion of elderly achieving the target AUC (64%), with, in particular, a considerable average increase of the dose (963 mg) among old patients underdosed at C1. Indeed, almost half of elderly (46%) were underexposed at C1 versus 25% at C2. In our study, dose adaptation upon overexposed or underexposure was not mandatory; in some situations, for clinical reasons, some practitioners have decided not to follow our recommendations of 5-FU dosing adjustment. For the second cycle, 25% of elderly underdosed did not had a dose increase as proposed, which could partly explain why still 25% of elderly patients are below the therapeutic range at C2. However, this observation is not different for younger patients. In fact, the proportion of underexposed, overexposed and well-exposed patients were identical between young and elderly patients at C2 and C3. The study of Wilhelm et al. [41], which enrolled 33 patients < 65 years and 42 patients ≥ 65 years with CRC receiving the weekly regimens of Arbeitsgemeinschaft Internistische Onkologie (AIO) (folinate, 5-FU), FUFOX (oxaliplatin, folinate, 5-FU) or the biweekly regimen of modified FOLFOX-6 (oxaliplatin, folinate, 5-FU), resulted in 64% of all patients under the therapeutic range, 33% of them well-dosed and 3% who were overexposed at the C1. In Saam's article [42], 5-FU AUC were monitored during 4 cycles in 64 CRC patients receiving any regimen in which 5-FU was administered over a period of 44–48 h. If necessary, a 5-FU PK-guided adjustment was performed after receiving the first 5-FU BSA-based dose. The first measurement indicated that 68% of patients were underexposed, 13% were in therapeutic range and 19% had an AUC over the superior target level. Based on our investigations and the results presented in the studies previously referred, we demonstrate that the vast majority of patients are not in the expected therapeutic range after receiving standard 5-FU BSA-based dose. The high interindividual variability after dose adaptation testifies of a very limited interest of the 5-FU BSA-based dosing. Upon 5-FU PK-guided dose adjustment in subsequent cycles, a significant decrease of this variability was observed.

Reports concerning tolerance of 5-FU–based chemotherapy in elderly patients are conflicting: some publications describe increase rates of stomatitis, nausea, diarrhoea, leukopenia or neutropenia [43–45], whereas no excess toxicity has been observed in others reports [33,34,46]. In our investigation, after receiving a standard 5-FU BSA-based dose, the frequency of diarrhoea, hand–foot syndrome and neutropenia was statistically similar between young and old patients. However, elderly tended to be more susceptible to severe mucositis than younger patients; the use of dental prosthesis and fixed implant, often linked to advanced age, is frequently responsible for inflammation of the oral mucosa [47,48] and could partly explain this higher proportion of elderly who presented serious mouth ulcers compared with young people. Diarrhoea and neutropenia were mostly severe toxicities observed among elderly overdosed patients; this observation is not surprising, given that numerous publication demonstrate the link between cytotoxic concentrations and the severity of neutropenia or diarrhoea [49,50]. Generally, we observed that grade III/IV toxicities were associated with a higher AUC than grade I/II. Conversely, almost twice as much toxicities were observed among patients overexposed than patients underexposed or well-exposed. As expected, the 5-FU PK-guided dose adjustment reduced the risk of adverse events, particularly severe toxicities. Lower incidence of grade III/IV were observed for the two groups between C1 and C3, and no grade IV toxicity was reported at C2 and 3 among elderly.

In an article by Sargent et al [33], a pooled analysis of 3351 patients from seven randomised phase 3 trials was performed. Patients who received 5-FU alone as adjuvant treatment were grouped into 10-year age ranges categories of equal size including a group older than 70 years. The study reported that treatment among elderly had the same benefit/risk ratio as for younger patient groups, with no statistically significant increase in toxicity. However, most of the time, clinical trials exclude elderly or include only highly selected old patients. For elderly patients with good performance Status (PS) and low CCI, there is evidence showing both efficacy and acceptable toxicity of chemotherapy [51], but what about the influence of these two parameters on toxicity in older people who are more frail? In our study, all elderly treated by 5-FU for a gastrointestinal cancer during the study period were included. Consequently, we believe that our study population is representative of the general elderly population, contrarily to what is observed in a clinical trial. For analyses, PS was not available for all the patients, but we were able to calculate CCI for elderly; 90% of them are having a CCI ≥ 6, which associated with a very important 10-year mortality rate [52]. As per the results by Jehn et al [53], in our study using 5-FU, the presence of comorbidity did not confer increased risk of toxicity or superior AUC values. Thus, we may consider that 5-FU PK dosing can improve the exposition and tolerability of 5-FU in elderly, regardless of clinical condition.

The main limitation of this work is that, at the time of the study, DPD genotyping or phenotyping were not available in our institution. Thus, dose adaptation at C1 based on these criteria was not possible. Nowadays, a pretherapeutic screening of DPD activity by pharmacogenetics is systematically performed. Patients with no DPD deficiency receive full dose, while the dose is decreased, as early as the first cycle, in agreement with *DPYD* variants for patients presenting a DPD deficiency. During the following cycles, the dose is adjusted as per the AUC and toxicity.

We demonstrated, throughout this work, the importance of considering interindividual variability of 5-FU exposure. However, efficacy of 5-FU is not only dependent on 5-FU metabolism but also by the use of folinic acid in association which acts as coactivator of the thymidylate synthetase, the main target of 5-FU. Even if folinic acid is associated to a limited degree with clinical outcomes [54], it should be emphasised that its interindividual variability was not considered for this study.

Generally, clinical trials exclude elderly or include highly selected old patients in terms of PS and comorbidity. In our study, all elderly treated by 5-FU for a gastrointestinal cancer during the study period were included. Consequently, despite a small number of patients (n = 31), we believe that they represent the general elderly population.

5. Conclusion

Overall, our analysis confirms that BSA-based dosing explains high 5-FU concentration variability among patients. The difficulty to predict 5-FU plasma levels for a given dose frequently led to ineffective concentrations or severe toxicities. PK-guided 5-FU dosing algorithm allowed 5-FU dose adaptation, leading to an improved tolerability while remaining within therapeutic concentration range. This tool, previously described as effective in the general population or young patients, is even more valuable for patients older than 75 years.

Ethics approval

All patients routinely underwent a blood analysis to evaluate their 5-FU exposure during the three first cycles. Consequently, no informed consent was required. However, data used in this article were recorded in such a manner that participants could not be identified. Patient confidentiality was maintained, and the protocol for data collection and analysis followed guidelines and were approved by our Institutional Review Board.

Availability of data

Data are available upon request to the corresponding author.

Conflict of interest statement

None declared.

Author contributions

F.G., L.B.-L. and A.S. contributed in study conception and design. J.V., V.Q., S.M., F.G. and L.B.-L. contributed in acquisition of data. P.M., K.M., F.G., L.B.-L. and A.S. analysed and interpreted the data. P.M. and A.S. drafted the manuscript. P.M., F.G., L.B.-L. and A.S. critically revised the manuscript. All authors gave the final approval.

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