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► To cite this version:

Pauline Macaire, Katarzyna Morawska, Julie Vincent, Valérie Quipourt, Sophie Marilier, et al.. Therapeutic drug monitoring as a tool to optimize 5-FU–based chemotherapy in gastrointestinal cancer patients older than 75 years. *European Journal of Cancer*, 2019, 111, pp.116 - 125. 10.1016/j.ejca.2019.01.102 . hal-03486193

HAL Id: hal-03486193

<https://hal.science/hal-03486193>

Submitted on 20 Dec 2021

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1 Therapeutic Drug Monitoring as a tool to optimize 5-FU based
2 chemotherapy in gastro-intestinal cancer patients of more
3 than 75 years

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20 *Keywords: elderly, 5-fluorouracil, gastrointestinal cancer, therapeutic drug monitoring*

21 ABSTRACT:

22 Aims

23 Most clinical trials exclude elderly people, leading to a limited understanding of the
24 benefit/risk ratio in this population. In despite existing data regarding the oncological
25 management of elderly receiving 5-FU-based regimen, our objective was to investigate 5-FU
26 exposure/toxicity relationship in patients ≥ 75 years and compare the effectiveness of 5-FU
27 Therapeutic Drug Monitoring between elderly and younger patients.

28 Methods

29 154 patients (31 of whom are over 75) with gastrointestinal cancers, who were to receive 5-
30 FU-based regimens were included in our study. At cycle 1, the 5-FU dose was calculated
31 using patient's Body Surface Area, then a blood sample was drawn to measure 5-FU
32 concentration and 5-FU dose was adjusted at the subsequent cycles based on cycle 1
33 concentration. Assessments of toxicity was performed at the beginning of every cycle.

34 Results

35 71% of elderly patients required dose adjustments after cycle 1, compared to 50% for
36 younger. Percentage of patients within 5-FU AUC range at cycle 2 was 64% and 68% for
37 respectively elderly and younger patients. The proportion of elderly patients experiencing
38 severe toxicities felt from 15% at cycle 1 to only 5% at cycle 3.

39 Conclusion

40 PK-guided 5-FU dosing algorithm, leading to an improved tolerability while remaining within
41 therapeutic concentration range, is even more valuable for patients over 75 years old than in
42 younger.

43 BACKGROUND

44 Since its original synthesis in the late 1950s, fluorouracil (5-FU) continues to be widely used
45 in the treatment of many cancers, including oesophagus, stomach, pancreas and colorectal
46 cancer (CRC) both as adjuvant therapy of early stage or in advanced setting (1, 2). Over the
47 last decades, knowledge improvement in 5-FU pharmacokinetics (PK) and mechanism of
48 action led to development of new treatments, based on the addition of the biomodulating
49 agent folinic acid, association with other cytotoxic drugs, or modification of 5-FU
50 administration schedule. Originally, 5-FU alone was delivered as a bolus. Nowadays,
51 administration by continuous intravenous infusion is used. Indeed, it was shown that this
52 delivery method increased 5-FU exposure duration, leading to an improved cytotoxic activity
53 and clinical effectiveness, while limiting toxicity (3-5). Despite these therapeutic progresses,
54 5-FU is often the source of severe treatment-related toxicities requiring hospitalization and
55 leading to death in 0.5% to 2% of cases (6-8).

56 The most well-known biochemical cause of intolerance to fluoropyrimidines is deficiency of
57 dihydropyrimidine dehydrogenase (DPD) (9, 10). DPD is defined as the first and rate-limiting
58 enzyme in the catabolic pathway of 5-FU, responsible for more than 80% of 5-FU elimination
59 (11, 12). Partial or complete deficiency in the DPD enzyme has been observed in 3-5% and
60 0.1% of the general population, respectively (13-15). DPD deficient patients experience
61 excessive and severe toxicity in the form of neutropenia, diarrhoea, mucositis and hand-foot
62 syndrome. Overall, DPD deficiency is observed in 39-61% of patients developing severe
63 toxicity (8, 16). In all patients, DPD deficiency is confirmed by sequence analysis of *DPYD*, the
64 gene encoding DPD, used as predictor of fluoropyrimidines-related toxicity when a
65 pathological mutation is found. To date, more than 30 sequence variations in the DPD gene

66 have been identified, with the most well-established variant being *DYPD*2A* (17, 18). To
67 improve efficacy and reduce toxicity, previous investigations focused on the relationship
68 between 5-FU plasma concentration and DPD activity to determine individual dose
69 adjustment in patients presenting DPD gene mutation (19-22). However, 5-FU
70 pharmacokinetic variability is affected by many others factors such as sex, disease status,
71 nutritional condition, organ function, co-medication, explaining frequent over and under-
72 exposure even though 5-FU dosage adjustment by *DYPD* genotype.

73 5-FU dosing is traditionally calculated according to Body Surface Area (BSA). Recent data
74 confirm the lack of scientific rational for 5-FU BSA-based dosing (23). As previously
75 demonstrated, there is no potential correlation between BSA and 5-FU plasma clearance
76 (24), possibly explaining the large 5-FU interindividual concentrations variation in patients
77 treated with standard schedule based on BSA. Because 5-FU is characterized by a strong
78 toxicity-exposure relationship and a narrow therapeutic window, the use of therapeutic drug
79 monitoring (TDM) approaches are greatly supported (25, 26). Some studies have
80 demonstrated successful strategies to monitor 5-FU blood concentrations and adjust
81 individual doses based on systemic exposure (27-30). Area Under the Curve (AUC) of 5-FU
82 concentrations is considered to be the most relevant pharmacokinetic parameter associated
83 to 5-FU-related efficacy and toxicity. Because of its intrinsic variability, it is generally
84 considered that an AUC range of 20 - 30 mg.h/L is required for successful therapy (31, 32). In
85 our centre, we have chosen to use an algorithm based on Gamelin's paper (29). Due to the
86 precision of 5-FU measurements, a small dose modification (i.e., $\pm 5\%$) would not have a
87 clinical or biological incidence, we extended the Gamelin's range of target AUC to 18-28
88 mg.h/L, to start dose adjustment at $\pm 10\%$.

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

99 To date, no initial 5-FU dose reduction is recommended for elderly patients but, in clinical
100 practice, empirical dose reductions or shorter chemotherapy regimens are often prescribed
101 in elderly patients because of the hypothetical risk of toxicity. Thus, the main objective of the
102 present study is to investigate exposure/toxicity relationship of 5-FU-based regimens in
103 individuals aged ≥ 75 years old. The secondary objective of this work is to compare the
104 effectiveness of 5-FU TDM between elderly and younger patients.

105 Patients & Methods

106 Population

107 This retrospective analysis was carried out in a database covering all patients diagnosed with
108 gastrointestinal cancer who received a 46h continuous 5-FU infusion from April 2014 to
109 February 2016 in the Dijon's Cancer Centre (Burgundy, France). The therapeutic follow-up in
110 our centre includes a blood sample analysis to determine 5-FU exposure during the three 1st
111 chemotherapy cycles. Patients eligible for this study were treated with specific digestive

112 cancer-treatment regimens by 5-FU infusion alone or associated with other cytotoxic ±
113 biotherapy for adjuvant or advanced therapy purposes. The data routinely collected include
114 gender, age, birth date, weight, height, Charlson Comorbidity Index (CCI) (elderly only),
115 primary tumor, type of treatment (metastatic or adjuvant), treatment line, chemotherapy
116 regimen, date of cycle, 5-FU bolus dose, 5-FU infusion dose, 5-FU concentration measured,
117 AUC calculated, proposed dose for the next cycle and toxicities. Individuals were classified
118 into two groups based on age: young group rounded up patients < 75 years old and elderly
119 included all patients ≥ 75.

120 **Study design and chemotherapy regimen adjustment**

121 At cycle 1 (C1), patients received folinic acid (400 mg/m²) by i.v. infusion over 2 h followed
122 by a 5-FU bolus (400 mg/m²) and immediately after by 46h continuous 5-FU infusion (2400
123 mg/m²) administered via a battery-operated pump. Patients could receive other cytotoxic
124 drugs and/or biotherapy before 5-FU regimen. Area Under the Curve (AUC) of 5-FU infusion
125 was calculated by multiplying the 5-FU steady-state concentration by the infusion duration
126 (46h). At the cycle 2 (C2), the dose of 5-FU infusion was determined according to an
127 algorithm derived from Gamelin's one, targeting AUC range of 18-28 mg.h/L. The same
128 methodology was applied at C2 to ensure correct exposure and perform dose adaptation at
129 the cycle 3 (C3) if necessary. Doses were to remain constant during the subsequent cycles,
130 except in case of severe toxicity. Clinicians were free to individually adapt any other drugs
131 doses included in the protocol.

132 **Blood sampling and plasma concentration determination**

133 To limit within-day variability of DPD activity (35), blood samples were taken between 8 and
134 10 a.m. the day following the beginning of 5-FU infusion. Samples were immediately

135 centrifuged and plasma kept frozen at -20°C until analysed. Plasma 5-FU concentrations
136 were determined by liquid chromatography. Chloro-uracil was used as internal standard. 5-
137 FU was extracted from the plasma with isopropanol-ethyl acetate (15/85 v:v) in the presence
138 of 200 mg ammonium sulfate to precipitate proteins. The organic phase was dried at 50°C
139 under nitrogen dioxide and reconstituted with 200 μL mobile phase before injection. Mobile
140 phase consisted of methanol/water (5/95 v:v). UV detection was performed at 265 nm. This
141 method was fully validated for routine measurement of 5-FU with a lower limit of
142 quantification of 30 $\mu\text{g/L}$.

143 Toxicities classification

144 All toxicities graded according to the NCI Common Terminology Criteria for Adverse Events
145 (CTCAE) (Version 4.0) and were clinically or biologically evaluated before each cycle with
146 particular attention to diarrhoea, neutropenia, mucositis and hand-foot syndrome. Severe
147 toxicity was defined as grade 3 or grade 4 toxicity.

148 Statistical methods

149 The distribution of patients' characteristics was expressed as percentages or mean values
150 presented as mean \pm SD (range) or median (range) if deemed appropriate. The statistical
151 analysis was conducted in patients older than 75 years or younger than 75 years. Univariate
152 analyses were performed. Quantitative data were analysed using Student's test or non-
153 parametric Mann-Whitney test for small sample size (effective < 30). Percentages were
154 compared using two proportions comparison test, Pearson's Chi-squared test for multiple
155 samples or Fisher's exact test for small sample size. The level of statistical significance was
156 set at $p = 0.05$. Most analyses were performed using SIGMAPLOT[®] software (Version 11.0,
157 SYSTAT Software, Inc).

158 RESULTS

159 Patient characteristics

160 A total of 154 patients with gastro-intestinal cancer were enrolled in our study. Thirty-one of
161 them were above 75 years or older and were included in the elderly group, whereas 123
162 were included in the younger adult group. Demographic data and study treatment details
163 are listed in Table 1.

164 The most frequent cancer which affects each group was the CRC (74% in elderly and 56.9%
165 in younger adult). Pancreas was the 2nd most frequent site (25.2%) in young adults, while
166 there was as much pancreatic cancer as stomach or oesophagus cancer (6.5%) in the elderly.
167 The proportion of patients treated in adjuvant and in metastatic settings was similar in both
168 groups. However, when only FOLFIRINOX regimens were considered, there was significantly
169 more treated patients (38.2%) in younger adults than in elderly (9.7%). Overall, elderly
170 patients received 28.2% less irinotecan-based chemotherapy than younger patients. It
171 should be noted that 67.7% of elderly were treated as first line therapy.

172 Interindividual variability in 5-FU pharmacokinetics

173 Figure 1 represents plasma 5-FU concentrations as a function of 5-FU-infusion dose
174 (calculated according to BSA) for each patient at C1. No proportionality between dose and
175 concentration was found. A considerable difference in blood concentrations was observed
176 for a same 5-FU dose in both groups. For example, in elderly, steady-state 5-FU
177 concentrations were ranging from 110 µg/L to 706 µg/L for an identical total dose of 4 000
178 mg. Similar conclusions could be drawn from younger patients but this variability seems to
179 be much more substantial among elderly. Consequently, the goal of 5-FU BSA dosing (i.e.,
180 bring all patients in the same target exposure) is not reached and those results confirm the

181 need to use another dose adjustment method than calculating 5-FU dose according to BSA
182 and more for elderly patients.

183 To confirm that 75 years old was a valuable cut-off, proportions of patients inside or outside
184 the 5-FU AUC range were compared for 4 age ranges (Table 2). AUC distribution was not
185 significantly different between the three youngest groups ($p = 0.920$). To note, there was no
186 patient over-exposed in the group of 55 years or less. On the contrary, the proportion of
187 patients ≥ 75 years well-exposed did not reach 30% (i.e., 24% less compared with 65-75
188 years group ($p = 0.039$)). Applying a cut-off value of 70 years would lead to no significant
189 difference in terms of proportion of patient well-exposed between 65-70 years (50%) and 70
190 years or more (40%) groups ($p = 0.386$). Same results were observed for under-exposed
191 patients (36% vs 42%, $p = 0.583$) and over-exposed patients (14% vs 18%, $p = 0.611$)
192 respectively. Thus, a cut-off value of 75 years was considered as pertinent.

193 Impact of 5-FU TDM and individual dose adjustment to reach target AUC 194 range

195 At C1 (i.e., with dose adapted according to BSA), the mean initial exposure for elderly
196 patients was 21.2 ± 10.1 mg.h/L and 20.2 ± 6.2 mg.h/L for younger adults with a 47% and
197 30% coefficient of variation (%CV) in each of the groups. Mean doses administered to elderly
198 ($4\ 239 \pm 418$ mg) were not significantly different from the ones administered to younger
199 adults ($4\ 234 \pm 536$ mg) ($p = 0.951$), which might explain why no difference was found
200 between AUC in the two groups ($p = 0.598$). However, when AUC %CV are compared
201 between C1 and C3 (i.e. after 2 cycles of TDM) an important decrease (- 20%) is observed for
202 elderly. This decrease is reflected a lesser AUC variability among individuals.

203 As shown in Figure 2, at C1, where the initial 5-FU infusion doses were calculated based on
204 BSA, only 29% of elderly presented an AUC within the therapeutic range, whereas 50% of
205 younger adults were within this same range ($p = 0.049$). Of the 13 elderly patients who were
206 under-dosed at cycle 1, 11 of them (85%) had a dose adjustment at cycle 2 with an average
207 increase of 963 mg (23%) compared to the mean initial dose of 5-FU. Interestingly, after 5-
208 FU PK-guided dosing adjustment, the percentage of elderly patients below the target AUC
209 decreased from 46% (13 of 28) to 25% (7 of 28) between cycle 1 and cycle 2 while the
210 percentage of elderly within the therapeutic range significantly increased from 29% (8 of 28)
211 at cycle 1 to 64% (18 of 28) at cycle 2 ($p = 0.011$). Similarly, the proportion of younger
212 patients who had an AUC within the therapeutic range progressed from 50% to 68%
213 between the two 1st cycles ($p = 0.008$). At cycle 2 and 3, there was no statistically significant
214 difference concerning proportion of under-, well- or over-exposed patients in both groups.

215 [Relation between 5-FU exposure and toxicity](#)

216 Main adverse events in the two groups were analysed at C1. All grades diarrhoea, hand-foot
217 syndrome, and neutropenia tend to be more frequent in the younger group as compared to
218 elderly, however differences were not statistically significant. The incidence of severe
219 mucositis (grade ≥ 3) was relatively low in both groups, but elderly tended to be more
220 exposed than younger patients (7.1% vs 2.7% respectively, $p = 0.024$).

221 At C1, 10% of elderly below or within AUC range declared severe toxicity compared to 29%
222 of those above AUC target. The only grade III/IV toxicities, below or within therapeutic AUC
223 range, declared among elderly patients were mucositis. Elderly patients above the AUC
224 range presented mostly neutropenia and diarrhoeas. The incidence of serious toxicities for

225 patients below or within AUC range did not differ significantly between the 2 groups ($p =$
226 0.905); as for patients above AUC range ($p = 0.683$).

227 All cycles combined, lower AUC values were observed for elderly presenting no toxicity or at
228 least non-severe (grade I/II) (21.3 ± 7.7 mg.h/L) compared to those presenting severe toxicity
229 (grade III/IV) (28.2 ± 7.7 mg.h/L) (Figure 3). Conversely, all cycles and grade combined,
230 patients over-dosed presented almost twice as much toxicities than patients under or well-
231 dosed (67.3% vs 35.8% respectively, $p < 0.0001$).

232

233 [Impact of 5-FU PK-guided dosing adjustment to reduce toxicity](#)

234 At C1 and C3, lower incidence of grade III/IV toxic effects was observed for both groups
235 (Figure 4). Decrease of severe toxicities was even more important for elderly (15% vs 5%
236 respectively). Of note, no grade IV toxicities at cycles 2 and 3 was observed in the elderly
237 group when compared to 1 during C1.

238 Seven young patients benefited from 5-FU bolus dose reduction between C1 and C2, due to
239 grade IV toxicities or hospitalisation during the inter-cycle. Among them, four patients had
240 also a 5-FU infusion reduction, while only 1 of them was over-exposed. Three elderly had
241 bolus dose reduction due to grade III adverse events ($N = 2$) and/or over-exposure ($N = 2$).
242 The 2 patients who had AUC above target benefited from an infusion dose reduction too.
243 Overall, all cycles combined, 3 out of 5 elderly and 5 out of 13 young patients presented
244 toxicities in spite of the absence of 5-FU bolus dose (mostly grade I/II for the 2 groups) and in
245 the absence of an over-exposure for most of them.

246

247 Relationship between Charlson Comorbidity Index (CCI) and PK or toxicity

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

253 DISCUSSION

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

270 Although 5-FU dosing is traditionally calculated according to BSA, a number of studies have
271 been conducted to evaluate an appropriate dose adjustment algorithm and to demonstrate
272 the advantage of 5-FU PK-guided dosing to reduce toxicity and enhance therapeutic
273 outcomes. Nevertheless, those studies mainly concerned young patients (< 65 years old) and
274 very few data exist for elderly ones. In our study, we have chosen to divide our population
275 by age range and evaluate 5-FU AUC range for each group to find optimal cut-off value of
276 age. Our data suggest that 75 years as a cut-off is better than the more frequently used 65 or
277 70 years. Indeed, we demonstrated that 5-FU BSA-dosing in 75 years or more patients is
278 even less suitable than in young people (only 29% of well-exposed with dose adapted
279 according to BSA), leading to a non-optimal treatment in this frail population. In this paper,
280 we show that 5-FU PK-guided dosing may help to reduce toxicity from cycle 1 to subsequent
281 cycle in elderly patients, and this, while increasing the dose in under-dosed patients.

282 At the 1st cycle, mean 5-FU doses administered to elderly ($4\,239 \pm 418$ mg) were not
283 different from those administered to young people ($4\,234 \pm 536$ mg). However, a difference
284 in terms of 5-FU combination was observed. Indeed, elderly received nearly 30% less
285 irinotecan-based chemotherapy (the cornerstone of 1st line metastatic CRC) than younger
286 patients, while 48% of them received a 1st line metastatic chemotherapy. This observation
287 suggests that oncologists, in our Cancer Centre, tend to favour less aggressive regimens
288 more than 5-FU dose reduction in elderly patients.

289 As a reminder, for this study, individual doses adjustment was based on systemic exposure
290 measured at the previous cycle. A range of 18-28 mg.h/L, based on Gamelin's algorithm (29),
291 was used as target AUC. Upon BSA-based dosing at cycle 1, only 29% of older than 75 years
292 group had a 5-FU AUC within the target range while 50% of young patients were within this

293 therapeutic range. This result leads to an important variability in 5-FU steady-state
294 concentrations, ranging, for example, from 110 µg/L to 706 µg/L for an identical total dose
295 of 4 000 mg for elderly. In comparison, PK-guided 5-FU dosing performed at cycle 2 resulted
296 in significantly higher proportion of elderly achieving the target AUC (64%), with, in
297 particular, a considerable average increase of the dose (963 mg) among old patients under-
298 dosed at C1. Indeed, almost half of elderly (46%) were under-exposed at cycle 1 versus 25%
299 at cycle 2. In our study, dose adaptation upon over- or under-exposure was not mandatory;
300 in some situations, for clinical reasons, some practitioners have decided not to follow our
301 recommendations of 5-FU dosing adjustment. For the second cycle, 25% of elderly under-
302 dosed did not had a dose increase as proposed, which could partly explain why still 25% of
303 elderly patients are below the therapeutic range at cycle 2. However, this observation is not
304 different for younger patients. In fact, the proportion of under-, over- and well-exposed
305 patients were identical between young and elderly patients at cycle 2 and 3. The study of
306 Wilhelm et al. (41), which enrolled 33 patients < 65 years and 42 patients ≥ 65 years with
307 CRC receiving the weekly regimens of AIO (folinate, 5-FU), FUFOX (oxaliplatin, folinate, 5-FU)
308 or the biweekly regimen of modified FOLFOX-6, resulted in 64% of all patients under the
309 therapeutic range, 33% of them well-dosed and 3% who were over-exposed at the cycle 1. In
310 Saam's paper (42), 5-FU AUC were monitored during 4 cycles in 64 colorectal cancer patients
311 receiving any regimen in which 5-FU was administered over a period of 44-48 hours. If
312 necessary, a 5-FU PK-guided adjustment was performed after receiving the first 5-FU BSA-
313 based dose. The first measurement indicated that 68% of patients were under-exposed, 13%
314 were in therapeutic range and 19% had an AUC over the superior target level. According to
315 our investigations and the results presented in the studies previously referred, we
316 demonstrate that the vast majority of patients is not in the expected therapeutic range after

317 receiving standard 5-FU BSA-based dose. The high interindividual variability following dose
318 adaptation testifies of a very limited interest of the 5-FU BSA-based dosing. Upon 5-FU PK-
319 guided dose adjustment in subsequent cycles, a significant decrease of this variability was
320 observed.

321 Reports concerning tolerance of 5-FU-based chemotherapy in elderly patients are
322 conflicting: some publications describe an increase rates of stomatitis, nausea, diarrhoea,
323 leukopenia, or neutropenia (43-45), whereas no excess toxicity have been observed in others
324 reports (33, 34, 46). In our investigation, after receiving a standard 5-FU BSA-based dose, the
325 frequency of diarrhoea, hand-foot syndrome, and neutropenia was statistically similar
326 between young and old patients. However, elderly tended to be more susceptible to severe
327 mucositis than younger patients; the use of dental prosthesis and fixed implant, often linked
328 to advanced age, is frequently responsible for inflammation of the oral mucosa (47, 48) and
329 could partly explain this higher proportion of elderly who presented serious mouth ulcers
330 compared with young people. Diarrhoea and neutropenia were mostly severe toxicities
331 observed among elderly over-dosed; this observation is not surprising given that numerous
332 publication demonstrate the link between cytotoxic concentrations and the severity of
333 neutropenia or diarrhoea (49, 50). Generally, we observed that grade III/IV toxicities were
334 associated with a higher AUC than grade I/II. Conversely, almost twice as much toxicities
335 were observed among patients over-exposed than patients under or well-exposed. As
336 expected, the 5-FU PK-guided dose adjustment reduced the risk of adverse events,
337 particularly severe toxicities. Lower incidence of grade III/IV were observed for the two
338 groups between cycle 1 and 3 and no grade IV toxicity was reported at cycle 2 and 3 among
339 elderly.

340 In Sargent's paper (33), a pooled analysis of 3 351 patients from 7 randomized phase 3 trials
341 was performed. Patients who received 5-FU alone as adjuvant treatment were grouped into
342 10-year age ranges categories of equal size including a group over 70 years old. Study
343 reported that treatment among elderly had the same benefit/risk ratio as for younger
344 patient groups, with no statistically significant increase in toxicity. However, most of the
345 time, clinical trials exclude elderly or include only highly selected old patients. For elderly
346 patients with good Performance Status (PS) and low Charlson Comorbidity Index (CCI), there
347 is evidence showing both efficacy and acceptable toxicity of chemotherapy (55), but what
348 about the influence of these two parameters on toxicity in older people more frail? In our
349 study, all elderly treated by 5-FU for a gastro-intestinal cancer during the study period were
350 included. Consequently, we believe that our study population is representative of the
351 general elderly population, contrarily to what is observed in a clinical trial. For analyses, PS
352 was not available for all the patients, but we were able to calculate CCI for elderly; 90% of
353 them having a $CCI \geq 6$, which associated with a very important 10-year mortality rate (56). As
354 Jehn's results (57), in our study using 5-FU, the presence of comorbidity did not confer
355 increased risk of toxicity or superior AUC values. Thus, we may consider that 5-FU PK-dosing
356 can improve the exposition and tolerability of 5-FU in elderly, regardless of clinical condition.

357 The main limitation of this work is that, at the time of the study, DPD genotyping or
358 phenotyping were not available in our institution. Thus, dose adaptation at cycle 1 based on
359 these criteria was not possible. Nowadays, a pre-therapeutic screening of DPD activity by
360 pharmacogenetics is systematically performed. Patients with no DPD deficiency receive full
361 dose, while the dose is decreased, as early as the first cycle, in agreement with *DPYD*
362 variants for patients presenting a DPD deficiency. During the following cycles, the dose is
363 adjusted according to AUC and toxicity.

364

365 We demonstrated, throughout this work, the importance of considering interindividual
366 variability of 5-FU exposure. However, efficacy of 5-FU is not only dependent on 5-FU
367 metabolism but also by the use of folinic acid in association which acts as co-activator of the
368 thymidylate synthetase, the main target of 5-FU. Even if folinic acid is associated to a limited
369 degree with clinical outcomes (58), it should be emphasized that its interindividual variability
370 was not considered for this study.

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

375

376 CONCLUSION

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

383 ADDITIONAL INFORMATION

384 **Ethics approval**

385 All patients routinely underwent a blood analysis in order to evaluate their 5-FU exposure
386 during the 3 first cycles. Consequently, no informed consent was required. However, data
387 used in this manuscript were recorded in such a manner that subjects could not be
388 identified. Patient confidentiality was maintained and the protocol for data collection and
389 analysis followed guidelines and were approved by our Institutional Review Board.

390 **Availability of data**

391 Data are available upon request to the corresponding author.

392 **Conflict of interest**

393 The authors declare no conflict of interest.

394 **Funding**

395 None

396 **Author contributions**

397 Study conception and design: FG, LBL, AS

398 Acquisition of data: JV, VQ, SM, FG, LBL

399 Analysis and interpretation of data: PM, KM, FG, LBL, AS

400 Drafting of manuscript: PM, AS

401 Critical revision: PM, FG, LBL, AS

402 Final approval: PM, KM, JV, VQ, SM, FG, LBL, AS

403 **Acknowledgments**

404 We thank Isabel Grégoire for language editing.

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590

591 **FIGURE LEGENDS**

592 **Figure 1** - Relationship between 5-FU plasma concentration and 5-FU continuous infusion dose at
593 cycle 1 in elderly and young patients.

594 **Figure 2** - Percentage of patients with 5-FU AUC values below, within or above the therapeutic range
595 at C1 and C2

596 **Figure 3** - Distribution of elderly patients presenting no toxicity or at least non-severe compared to
597 those presenting severe toxicity according to AUC values

598 **Figure 4** - Percentage of elderly and young patients developing severe adverse events at C1 and C3

600 **Table 1** - Initial patients characteristics and treatment regimens (NS : non significant)

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 \pm SD (range)	69.5 \pm 15.1 (35-115)	70.9 \pm 13.3 (47-109)	NS
HEIGHT , cm, mean \pm SD (range)	168.9 \pm 8.4 (150-186)	166.4 \pm 8.2 (150-182)	NS
CHARLSON COMORBODITY 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
Esophagus	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
BIOOTHERAPY , 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

601

602

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

AUC RANGE	< 55 YR	55 – 65 YR	65-75 YR	≥ 75 YR
<i>Below (%)</i>	53	39	36	46
<i>Within (%)</i>	47	51	53	29
<i>Above (%)</i>	0	10	11	25

605

Figure 1

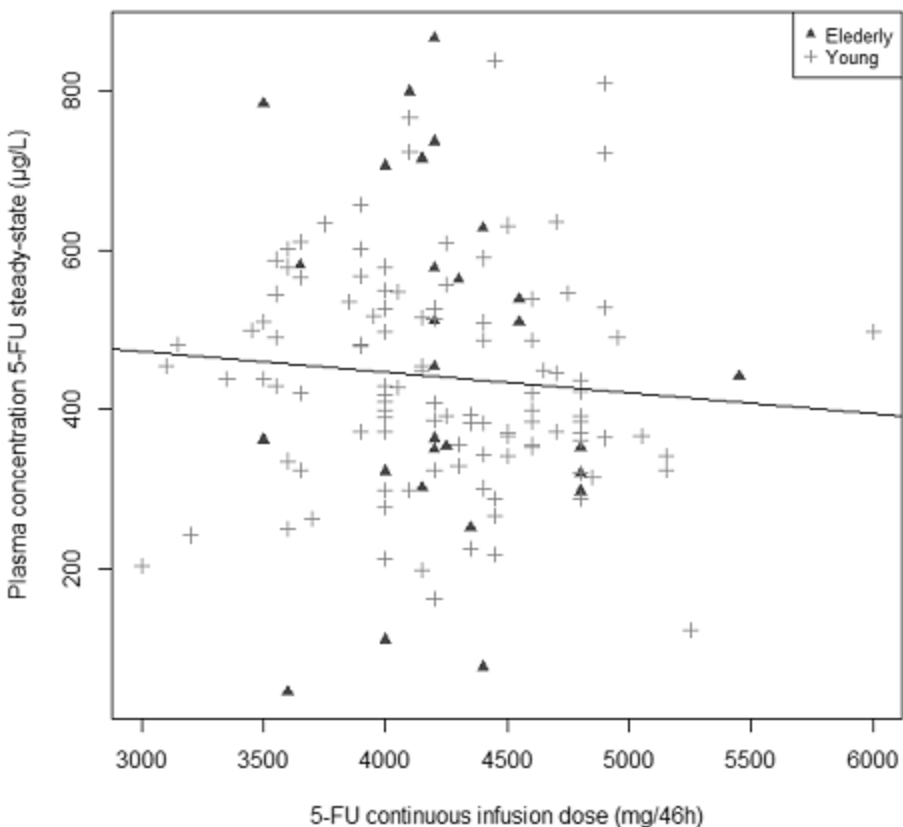


Figure 2

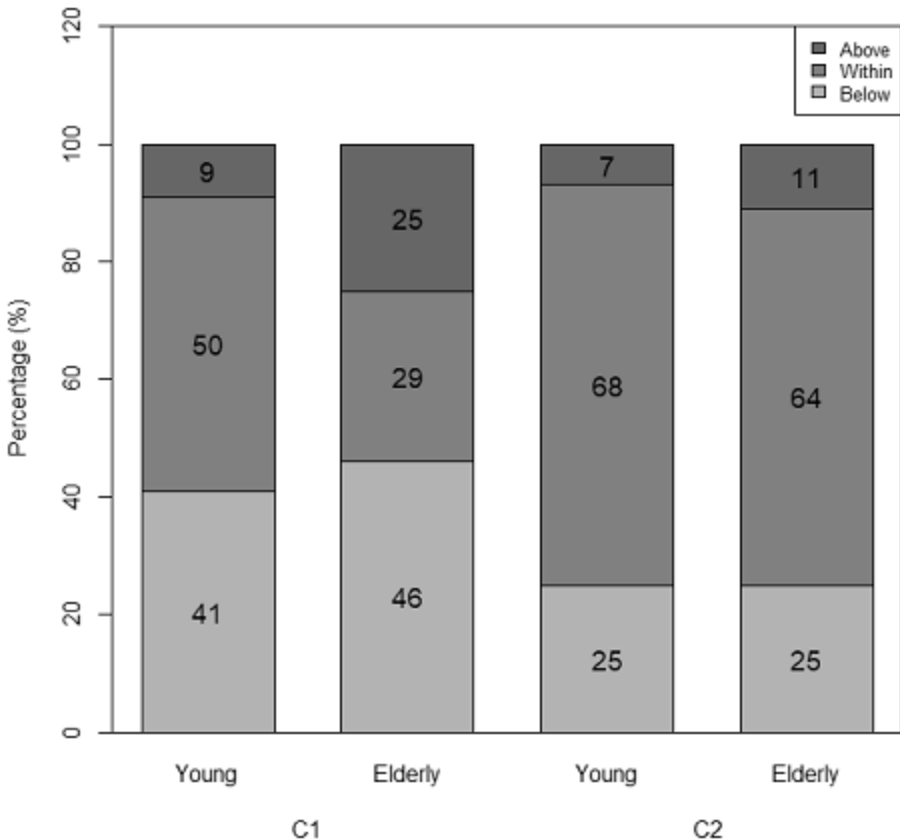


Figure 3

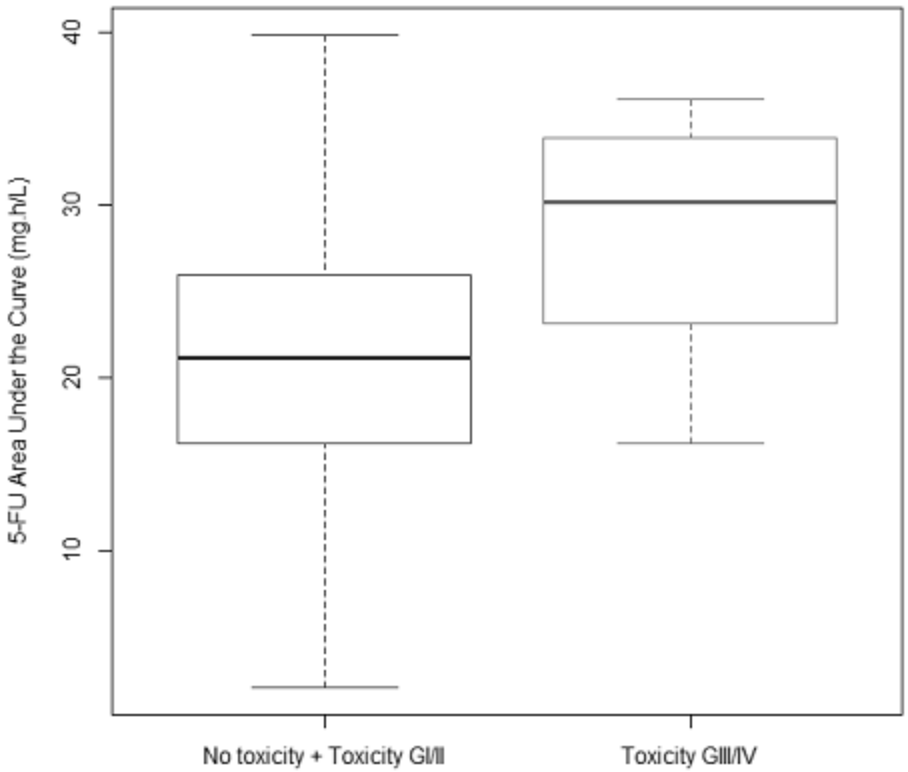


Figure 4

