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## Toxicities associated with chemotherapy regimens containing a fluoropyrimidine: A real-life evaluation in France

Chantal BARIN-LE GUELLEC<sup>1,2</sup>, Claire LAFAY-CHEBASSIER<sup>3,4</sup>, Isabelle INGRAND<sup>3,5</sup>, Jean-François TOURNAMILLE<sup>6</sup>, Adeline BOUDET<sup>7</sup>, Marie-Christine LANOUE<sup>7</sup>, Gautier DEFOSSEZ<sup>5</sup>, Pierre INGRAND<sup>5</sup>, Marie-Christine PERAULT-POCHAT<sup>3,4</sup>, Marie-Christine ETIENNE-GRIMALDI<sup>8</sup>.

- 1) Laboratoire de Biochimie et Biologie moléculaire, unité de pharmacogénétique ; CHU de Tours, FRANCE
- 2) INSERM U1248-IPPRIT ; Université ; CHU de Limoges, FRANCE
- 3) Service de Pharmacologie clinique et Vigilances; Université; CHU de Poitiers FRANCE
- 4) INSERM U1084-LNEC/ INSERM CIC 1402; Université; CHU de Poitiers FRANCE
- 5) Unité d'Epidémiologie et Biostatistique, Registre Général des Cancers Poitou-Charentes; INSERM CIC 1402; Université; CHU de Poitiers FRANCE
- 6) Unité de Biopharmacie Clinique Oncologique, Pharmacie; CHU de Tours, FRANCE
- 7) OMEDIT région Centre; CHU de Tours, FRANCE
- 8) Centre Antoine Lacassagne, Nice, FRANCE

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### Corresponding author:

Chantal BARIN-LE GUELLEC

Pharmacogenetics unit, Department of Biochemistry, University hospital of Tours, 2 boulevard Tonnellé, 37044 TOURS cedex, France

e-mail : [chantal.barin-leguellec@univ-tours.fr](mailto:chantal.barin-leguellec@univ-tours.fr)

Phone: +33-2-47-47-80-60

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### Highlights :

- Early incidence rate of serious adverse events with fluoropyrimidines is 19.3%
- The number of FP-related toxic deaths is estimated around 150/year in France
- Death, life-threatening prognosis or incapacity affect 1200 patients/year in France
- These are declared to a pharmacovigilance center in only 12.5% of cases
- Systematic pre-therapeutic screening of DPD deficiency is urgently needed.

## ABSTRACT

11 ***Aims:***

12 Despite fluoropyrimidines remain major drugs still present in 50% of chemotherapies for solid  
13 tumour treatments, incidence data for FP-related toxicity are poorly documented in real life. This  
14 study evaluate the number of patients receiving FP-based chemotherapies in France, along with the  
15 true incidence of FP-related serious adverse effects (SAEs) before recent mandatory DPD-screening  
16 introduced by French Health Authorities.

17 ***Methods:***

18 Exhaustive data on the number of patients treated with FP-based chemotherapy in 2013-2014 were  
19 collected in the *Centre-Val de Loire* region of France. True incidence of SAEs was extracted from a  
20 cohort of 513 patients with incident solid tumours receiving first-line FP-based chemotherapy.

21 ***Results:***

22 After extrapolation at national level, we estimated that 76,200 patients are currently treated  
23 annually with 5FU (53,100 patients, 62% digestive vs 26% breast vs 12% head and neck cancers) or  
24 capecitabine (23,100 patients, 45% digestive vs 37% breast cancer vs 18% non-documented). Early  
25 (first two cycles) SAE incidence rate was 19.3% (95%CI 16-23%) including one toxic death (0.2%,  
26 95%CI 0-1%). SAE incidence rate was 32.2% (95%CI 28-36%) over the first six months of treatment.  
27 Incidence of death, life-threatening prognosis or incapacity/disability was 1.4% (95%CI 0.4-2.4%)  
28 and 1.6% (95%CI 0.5-2.6%) during first two cycles and first six months, respectively.

29 ***Conclusion:***

30 These data highlight the significant public health issue related to FP toxicity, with around 1,200  
31 patients developing FP-related life-threatening prognosis or incapacity/disability annually in France,  
32 including 150 toxic deaths. It is hoped that DPD-deficiency screening will reduce such iatrogenic  
33 events and eradicate toxic deaths.

34

## 35 INTRODUCTION

36 Fluoropyrimidines (FP), i.v. 5-fluorouracil (5FU) and its oral prodrug, capecitabine, entail severe  
37 grade 3-4 toxicities (mainly hematological and digestive) in 10% to 30% of patients, depending on  
38 the chemotherapy regimen, and lead to toxic deaths in 0.1% to 1% of patients (1–8). Surprisingly,  
39 accurate toxicity incidence data are poorly documented in real-life settings. In France, adverse  
40 effects (AE), serious AE (SAE), and even toxic deaths are not clearly documented due to under-  
41 reporting to the regional pharmacovigilance centres (CRPV). Deficiency in dihydropyrimidine  
42 dehydrogenase (DPD), the key enzyme of 5FU catabolism, likely accounts for between 20% and 60%  
43 of FP-related early severe toxicities (1–3,9,10) and consensual deleterious *DPYD* polymorphisms  
44 would explain up to 20-30% of FP-related severe toxicities (11). It is estimated that 3% to 5% of  
45 Caucasians are carriers of a major DPD-deficiency, and that 0.1 to 0.3% present complete deficiency  
46 (12,13). Since the publication of the first case in 1985 describing a 5FU-related toxic death of a  
47 patient presenting profound DPD deficiency (14), numerous publications have repeatedly  
48 demonstrated a causal link between DPD deficiency and occurrence of severe or fatal toxic events  
49 in patients treated with 5FU or capecitabine (4,9,10,15–18). Two recent prospective studies have  
50 demonstrated the feasibility and usefulness of individual FP-dose adaptation based on *DPYD*  
51 genotype for reducing FP-related toxicities (5,19).

52 DPD deficiency screening is currently performed using either genotyping or phenotyping, or a  
53 combination of both (13,20). Many European countries recommend pre-therapy screening for DPD  
54 deficiency and mandatory DPD screening is currently being discussed at European level with a view  
55 to modifying 5FU and capecitabine labels accordingly. French health authorities recently made  
56 mandatory the routine determination of DPD deficiency based on measurement of plasma uracil  
57 concentrations prior to FP-based chemotherapies (21). The objective of this study was to evaluate  
58 the number of patients receiving FP-based chemotherapies in France along with the true incidence  
59 of FP-related SAEs before widespread implementation of DPD-screening recommendations. Such  
60 data may serve as a reference for future evaluation of the clinical impact of French  
61 recommendations.

62

## 63 MATERIAL AND METHODS

## 64 **Evaluation of the number of patients receiving FPs in France**

65 In France, capecitabine is almost exclusively delivered by non-hospital pharmacies (including health  
66 institution prescriptions). In contrast, 5FU is delivered only by health-care institutions. Exhaustive  
67 information on the number of patients treated with FP-based chemotherapy in 2013 and 2014 was  
68 collected in the *Centre-Val de Loire* area of France and was further extrapolated at national level.

### 69 Capecitabine consumption in the Centre-Val de Loire area

70 Capecitabine consumption data were obtained from the French national claims database  
71 (SNIIRAM). Data collected were: number of patients receiving capecitabine, age, sex, cancer  
72 location and the status of the prescribing institution (private/public).

### 73 5FU consumption in the Centre-Val de Loire area

74 The number of i.v. 5FU preparations delivered by pharmacies within private and public health-care  
75 institutions was recorded, along with a description of the chemotherapy protocol, number of cycles  
76 and cancer site. Data were automatically extracted from the pharmacies' software and analysed  
77 using QlicView®. To ensure complete data collection and consistent checking, extracted results  
78 were compared with true FP consumption data as declared by each institution to the Observatory  
79 for Medication, Medical Devices and Therapeutic Innovation (OMEDIT) of the *Centre-Val de Loire*  
80 area. This also allowed consumption data to be estimated for the few institutions which did not  
81 convey their data, based on their relative consumption at regional level.

## 82 **Evaluation of the true incidence of SAEs under FPs**

### 83 Data collection

84 Data were extracted from the SIRCADE study cohort (22). The objective was to assess the incidence  
85 of post-chemotherapy SAEs in patients diagnosed receiving first-line chemotherapy. This cohort  
86 was established by random selection of 4,000 patients out of 12,000 with incident solid tumour in  
87 2012 in the general *Poitou-Charentes* area cancer registry. Among these 4,000 patients, 1,024  
88 received chemotherapy during the first 6 months of treatment, and 513 (12.8 %) received a FP  
89 (capecitabine, 5FU, UFT). Pharmacists trained in pharmacovigilance systematically screened  
90 patients' medical files to detect SAEs during the 6 months after initiation of the FP-based  
91 chemotherapy. AEs were defined as "*all deleterious undesirable reactions resulting from the*  
92 *authorized use of the medication at normal dosages, harmful reactions resulting from medication-*

93 *related errors, and usages non-compliant with the terms of the authorization to market, including*  
94 *drug misuse and abuse” (23). SAEs were defined as “any AE entailing hospitalization or*  
95 *prolongation of hospital stay, permanent disability or invalidity, life-threatening prognosis and*  
96 *death”.* This pharmacovigilance-specific definition differs from the 0-5 toxicity grade based on  
97 clinical features and symptoms generally used in oncology. Any medically significant effect,  
98 cancellation or postponement of chemotherapy were documented, along with SAE accountability  
99 (WHO rules) (24). Clinical data (weight, height, body mass index, Charlson morbidity score),  
100 chemotherapies administered (drug name, dosage, starting and termination dates) and notification  
101 to the CRPV, if any, were collected, along with SAEs (date and mode of occurrence, clinical and  
102 paraclinical data, corrective treatment) and patient evolution.

### 103 Evaluation of SAE incidence rates

104 SAE incidence rates, corresponding to the number of patients experiencing at least one SAE  
105 attributed to FP, were calculated with 95% confidence intervals (95%CI).

106

## 107 **RESULTS**

### 108 **Capecitabine consumption in the Centre-Val de Loire area**

109 An annual average of 890 patients was treated with capecitabine (851 in 2013, 930 in 2014).  
110 Capecitabine consumption mainly concerned digestive (45%) and breast cancers (37%), with 18% of  
111 prescriptions for other or non-documented cancers. Patient age ranged from 20 to 90 years and  
112 65% of prescriptions concerned women.

### 113 **5FU consumption in the Centre-Val de Loire area**

114 Prescription data were obtained for 19 health institutions among the 23 with chemotherapy  
115 activity. The 4 institutions which did not supply data represented 16.9% of the regional  
116 consumption (OMEDIT data), giving a completeness rate for extracted data of 83.1%. On average,  
117 1,707 patients per year received 5FU-based chemotherapy (**Table 1**). After correction by the  
118 completeness rate, this gave an annual mean of 2,050 patients treated by intravenous 5FU in the  
119 *Centre-Val de Loire* area. Given the heterogeneity of protocol names (579), 18 “standardized  
120 protocols” were defined following regrouping and harmonization. **Table 2** lists the annual number  
121 of patients and administered cycles, according to protocols and cancer location. On yearly average,

122 5FU was administered in 1,066 digestive tumours (62%), 401 breast cancers (26%), and 206 head  
123 and neck cancers (12%).

## 124 **Incidence and typology of FP-related adverse effects**

### 125 Description of patients

126 Among the 513 patients from the SIRCADE study (55.4% women, mean age 62.3 years, range 26-  
127 92), a large majority (91.2%) were given i.v. 5FU, and only 9.7% received capecitabine (2.1%  
128 received both drugs sequentially) (Table 3). Mean Charlson score was 2.56 (range 0-12). The  
129 majority of patients (53.3%) had digestive cancer, 32.9% breast cancer and 9.6% head and neck  
130 cancers. Eighteen patients (3.5%) had multiple cancer sites. One hundred and fifty patients (29.2%)  
131 exhibited advanced disease. A total of 495 patients (96.5%) received a FP from the beginning of  
132 treatment, and two from the second cycle. Among the 495 patients receiving a FP from the  
133 beginning of treatment, only 63 (12.7%) received a FP alone. Chemotherapy protocols are  
134 described in Table 4. Fifteen out of 513 (2.9%) patients benefited from pretherapeutic DPD-  
135 deficiency screening (genotyping and/or uracilemia-based phenotyping).

### 136 Incidence and description of FP-related SAEs during the first two FP cycles

137 Among the 497 patients receiving a FP from the first or second chemotherapy cycle, 96 experienced  
138 at least one SAE during the first two FP cycles, giving an early incidence rate of 19.3% [95%CI 15.8%-  
139 22.8%]. Two patients were found to be DPD-deficient and received a reduced dosage. None  
140 exhibited SAE. Among the observed 116 SAE (107 with 5FU, 6 with capecitabine, 2 with UFT, 1 with  
141 5FU+capecitabine), 53.4% were hematologic, 12.9% were gastro-intestinal and 6.9% affected the  
142 nervous system (Table 5). This table also illustrates that the protocols most often involved in  
143 toxicity were FEC (5FU, cyclophosphamide and anthracycline) and those including 5FU + platinum  
144 derivatives. However, these protocols are also the most prescribed (Table 4). When combining  
145 prescription data (table 4) and toxicity data (table 5), the most toxic regimen (incidence of toxicity,  
146 %) were FP + platinum derivative + targeted therapy (75%), followed by FP + platinum derivative +  
147 taxane (47%), and FP + platinum derivative (24.5%). FEC regimen was associated with a toxicity rate  
148 of 13% and no SAE occurred in the 18 patients who received FU or FUFA alone. Capecitabine alone  
149 was found to be responsible for cardiac toxicity as well as for cutaneous and digestive disorders. Its  
150 overall toxicity rate was 15%. As expected, neurotoxicity was only observed with chemotherapies  
151 containing a platinum derivative, reaching a toxicity rate of 3.2%.

152 One toxic death (0.2% incidence rate, 95%CI 0.0-1.1) was observed (febrile neutropenia) at cycle 2  
153 of a palliative chemotherapy combining 5FU-carboplatin-cetuximab in a 62-year-old patient with a  
154 Charlson score of 3 presenting with pharyngeal cancer and bone metastases. In six other patients (5  
155 receiving 5FU and 1 capecitabine), SAEs led to a life-threatening prognosis or incapacity/disability  
156 (Table 6). The overall incidence of early death, life-threatening prognosis or incapacity/disability  
157 thus reached 1.4% (7/497, 95%CI 0.4-2.4%). Among the 495 patients receiving a FP from the  
158 beginning of treatment, 8 (1.6%) did not receive FP at second cycle: for 5 of them (1%), the FP (5FU  
159 in 3 patients, capecitabine in 2 patients) was withdrawn following SAE (stroke with sequelae, chest  
160 pain related to coronary spasm, chest pain, myocardial infarction and  
161 asthenia/neutropenia/mucositis, respectively).

#### 162 Incidence and description of FP-related SAEs during the first six months

163 Among the 513 patients, 165 presented at least one FP-related SAE during the first six months of  
164 chemotherapy, giving an overall incidence of 32.2% [95%CI 28.1-36.2]. One patient exhibited a life-  
165 threatening SAE at cycle 3 (Table 6), resulting in an overall incidence of FP-related death, life-  
166 threatening prognosis or incapacity/disability at 6 months of 1.6% (8/513, 95%CI 0.5-2.6). Only 2  
167 SAEs occurring during the first 6 months were notified to a CRPV. Among the 8 SAEs leading to  
168 death, incapacity/disability or life-threatening prognosis, only one was declared. This finding  
169 confirms the extremely high rate of non-declaration of chemotherapy-associated SAEs.

#### 170 **Extrapolation of the annual number of FP-related SAEs in France**

171 Based on an annual total of 2,940 cancer patients receiving FP-based chemotherapy in the *Centre-*  
172 *Val de Loire* area (890 capecitabine, 2,050 5FU), national extrapolation was based on 2014 data  
173 from the French Institute for Statistics and Economic Studies (INSEE) showing 65,907,000  
174 inhabitants for the whole country relative to 2,577,000 inhabitants in the *Centre-Val de Loire* region  
175 (i.e. 3.91%). Such an extrapolation is justified by the fact that cancer incidence is very similar  
176 between the *Centre-Val de Loire* region and the entire French nation (Table 7), but also by the  
177 homogeneity of French clinical practices via recommendations of clinical societies. It is thus  
178 estimated that 75,200 patients were treated with FP in France in 2014. Considering a French  
179 population growth rate of 1.29% between 2014 and 2019 (INSEE data), it is thus estimated that  
180 around 76,200 patients are currently treated annually in France with 5FU (53,100 patients) or  
181 capecitabine (23,100 patients). Regarding capecitabine, this figure is confirmed by open-data



182 sources (Open-Medic) from the French Health Insurance database (The *Système National des*  
183 *Données de Santé* (SNDS)), which summarizes the number of patients who received this drug over  
184 the past five years (**Figure 1**), illustrating that prescription of capecitabine have not changed over  
185 recent years.

186 Considering a FP-related SAE incidence of 32.2% during the first 6 months of treatment, the  
187 expected number of patients presenting a SAE in France is estimated at 24,500 per year [95%CI  
188 21,400-27,600]. Focusing on the first two cycles (19.3% SAE incidence), the expected number of  
189 patients with early toxicity is 14,700 per year [95%CI 12,000-17,400]. The estimation of patients  
190 with SAEs entailing death, life-threatening prognosis or incapacity/disability (1.6% over the first 6  
191 months) is approximately 1,200 patients per year [95%CI 380-1,980], of which 1,050 have early  
192 toxicity. The number of FP-related toxic deaths in France is estimated around 150 per year [95%CI  
193 0-820].

194

## 195 **DISCUSSION**

196 Results of the present FP consumption study conducted in the *Centre-Val de Loire* region,  
197 extrapolated to national level, estimate the annual number of cancer patients treated with FP-  
198 based chemotherapy in France at roughly 53,000 for 5FU and 23,000 for capecitabine, totalling  
199 76,000 patients. This figure may be slightly overestimated since some patients possibly received  
200 both 5FU and capecitabine (information unavailable due to separate anonymized databases for 5FU  
201 and capecitabine consumption). The pharmacovigilance SIRCADE study using the 2012 general  
202 cancer registry of the *Poitou-Charentes* region showed that 12.8% (513/4000) of patients with  
203 incident solid tumours received FP-based chemotherapy, consisting of 5FU in 91.2% of cases. As  
204 12,000 patients were included in this registry, the number of patients receiving 5FU in *Poitou-*  
205 *Charentes* is thus estimated at 1,400 for 2012. Considering INSEE data indicating that the *Poitou-*  
206 *Charentes* region represented 2.73% of the whole country in 2012, along with a 2.33% population  
207 growth from 2012 to 2019, the annual number of patients currently treated with 5FU nationwide is  
208 thus estimated at 52,500. Of note, the consumption and pharmacovigilance studies are very  
209 concordant regarding the national estimation of patients currently treated annually with 5FU-based  
210 chemotherapies in France. The pharmacovigilance SIRCADE study also highlights the still significant  
211 place of FP in the chemotherapeutic arsenal of solid cancer treatments: FPs were administered in

212 50% of patients with incident solid tumour treated by chemotherapy, and 96% of them received FP  
213 from the first chemotherapy cycle.

214 The goal of the pharmacovigilance study was to document FP-related toxicities during the first six  
215 months of chemotherapy. In this 2012 cohort study, 5FU was administered to the vast majority of  
216 patients, with only 9.7% receiving capecitabine and 2% UFT. Imputability of FP was carefully  
217 checked. However, as FPs are associated with other chemotherapeutic agents and/or targeted  
218 therapies in 87.7% of patients, present data must be interpreted in this context. SAEs related to FP-  
219 based chemotherapies over the first six months of treatment represented 32.2% and early SAEs  
220 19.3%. A focus on early SAEs observed according to the type of FP showed that SAE rate was 19.8%  
221 [95%CI 16.1-23.5] in the 439 patients receiving 5FU vs 16.2% [4.3-28.1] in the 37 patients receiving  
222 capecitabine vs 33.3% [95%CI not assessable] in the 6 patients receiving UFT (unshown data). As  
223 described above, the toxicity rate of FP-based chemotherapy regimens varied widely from one  
224 protocol to another, those combining a FP, a platinum derivative and a targeted therapy being the  
225 most toxic. No SAE was observed when 5FU was administered alone or associated with folinic acid.  
226 This confirms that toxicities observed with FP-based regimens are favoured by their association  
227 with the other drugs. In contrast, 15% of patients taking capecitabine alone exhibited a SAE,  
228 indicating that this molecule presents a risk by itself. The low rate of neurological SAE is in line with  
229 the cumulative nature of these adverse events the incidence of which is low at the beginning of  
230 treatment and increases with cycle numbers. Importantly, the incidence rate of SAEs leading to  
231 death, life-threatening prognosis or incapacity/disability was 1.6%, including 0.2% toxic deaths. Of  
232 note, 88% (7/8) of these SAEs occurred during the first 2 chemotherapy cycles. With the exception  
233 of peripheral neuropathy, likely linked to oxaliplatin (patient #2), most observed SAEs leading to  
234 death, life-threatening prognosis or incapacity/disability were typical of FP toxicity ([Table 6](#)).  
235 However, the majority of these SAEs are likely not triggered by DPD deficiency. In fact, 4 out of  
236 these 8 SAEs were myocardial infarction or ischemic stroke, which are known to be independent  
237 from DPD deficiency (25). In contrast, the SAEs observed in both the deceased patient (febrile  
238 neutropenia) and in patient #3 (mucositis, thrombopenia, neutropenia) is evocative of DPD  
239 deficiency since these complications are known to be related to 5FU pharmacokinetics and  
240 occurred from the first chemotherapy cycle. Unfortunately, DPD-deficiency screening was not  
241 performed in these patients.

242 Surprisingly, among the 8 SAEs involving a life-threatening prognosis or leading to  
243 incapacity/disability, only one (i.e. 12.5%) was declared to a CRPV. This strongly confirms the  
244 extremely elevated rate of SAE under-reporting, even in cases of very severe SAEs. Thus, the  
245 quantitative and qualitative data in the national pharmacovigilance base retrieved from  
246 spontaneous declarations clearly do not reflect real life.

247

## 248 **CONCLUSIONS**

249 Our final objective was to make an accurate assessment of the number of patients at risk of  
250 developing FP-based chemotherapy related SAEs in France. Based on the above results, around  
251 24,500 patients per year run the risk of SAE during FP-based chemotherapy in France, 14,700 of  
252 which during the first 2 cycles. Regarding 5FU administration, these figures are 17,100 and 10,250,  
253 respectively. Since oncologic physicians are used to handling SAEs not entailing a life-threatening  
254 prognosis, a more relevant datum is the annual number of patients developing SAE involving a life-  
255 threatening prognosis or incapacity/disability, presently estimated at 1,220 patients in France,  
256 including approximately 150 toxic deaths. Based on the present observation that two out of the 8  
257 SAEs carrying a life-threatening prognosis or incapacity/disability were likely linked to DPD  
258 deficiency, the rate of severe iatrogenic events related to DPD deficiency is around 0.39% (2/513)  
259 and would thus concern around 300 patients annually in France. Although regional disparities may  
260 exist, very few patients are currently explored for DPD-deficiency (2.9% in our cohort). Data from  
261 the French *Agence de la Biomédecine* confirms that 3387 patients were screened for DPD deficiency  
262 (restricted to *DPYD* genotyping) in 2014 (i.e. about 4.4% of patients who received a FP) but also  
263 illustrates the regular increase of this practice (3321 patients genotyped in 2015, 4481 in 2016 and  
264 5498 in 2017). It is hoped that recent French recommendations advocating mandatory DPD-  
265 deficiency screening (21) will dramatically reduce severe FP-related iatrogenic events and help  
266 eradicate toxic deaths.

267

**Conflict of interest statement:** None.

**Legends of figures:**

**Figure 1:** Number of patients receiving capecitabine each year between 2014 and 2018, as obtained from the Open-Medic open-data source, from the French health Insurance system.

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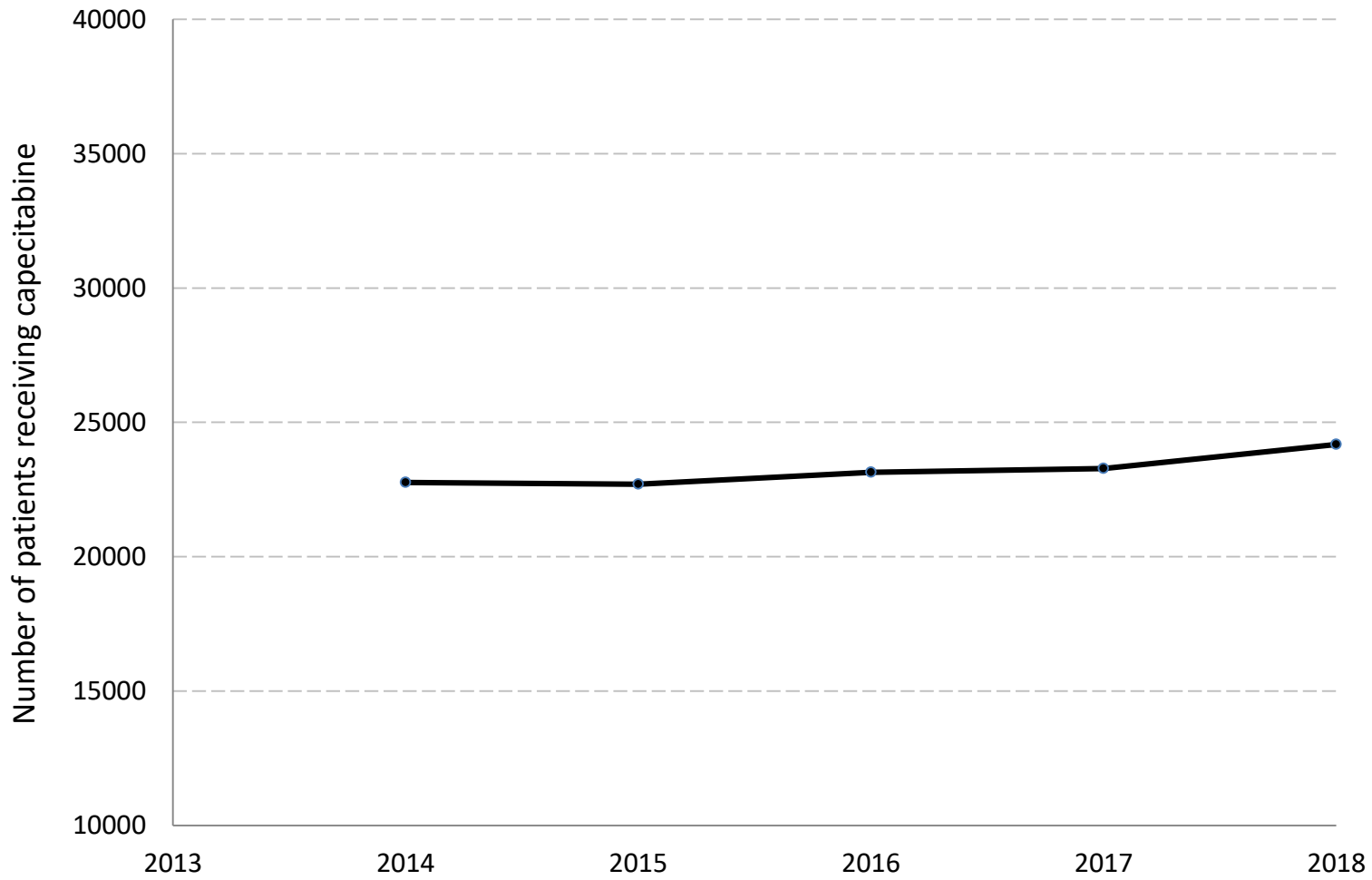




Table 1: 5FU consumption data extracted from pharmacy software of 19 health institutions in 2013 and 2014

<b>Year</b>	<b>Number of patient</b>	<b>Number of 5FU preparations</b>	<b>Number of 5FU cycles</b>	<b>Mean number of cycles per patient</b>
2013	2037	19884	11739	5.8
2014	1984	20021	11682	5.9
Sum 2013+2014	3414 *	39905	23421	
Annual mean	1707	19953	11711	

\* Since 607 patients received 5FU in 2013 and 2014, the sum of patients does not equal the arithmetic sum of 2013+2014.

Table 2: 5FU consumption data (2013-2014): Annual mean number of patients receiving i.v. 5FU per cancer localisation and protocol

Standardized protocols	Mean number of patients/year				Mean number of cycles/patient
	Digestive cancer	Breast cancer	Head&neck cancer	Total * N (%)	
5FU or FUFA + platinum derivative	542	1	105	648 (30.8%)	5.8
5FU + cyclophosphamide + anthracycline (FEC)		415		415 (19.8%)	3.1
5FU or FUFA + irinotecan + targeted therapy	208			208 (9.9%)	8.2
5FU or FUFA + irinotecan	186			186 (8.9%)	6.2
5FU or FUFA + platinum derivative + targeted therapy	146		38	184 (8.8%)	7.0
5FU or FUFA (LV5FU2 or Mayo regimen or other) alone	141	3		144 (6.9%)	5.8
5FU or FUFA + irinotecan + platinum derivative	107			107 (5.1%)	6.4
5FU or FUFA + platinum derivative + taxane	8		70	78 (3.7%)	5.1
5FU or FUFA + targeted therapy	42			42 (2.0%)	7.3
5FU or FUFA + other chemotherapies	39			39 (1.9%)	4.1
5FU + navelbine		35		35 (1.7%)	4.4
5FU or FUFA + platinum derivative + anthracycline	6			6 (0.3%)	3.5
5FU or FUFA + irinotecan + taxane	3			3 (0.1%)	3.7
5FU + cyclophosphamide + antimétabolite		3		3 (0.1%)	8.3
5FU or FUFA + taxane	1		1	2 (0.1%)	1.5
5FU or FUFA + irinotecan + platinum derivative + targeted therapy	1			1 (0%)	1.0
All protocols*	1066	451	206	1707*	

FUFA means 5FU associated with Folinic Acid.

\* Since 378 patients received more than one protocol, the sum of patients per localisation does not equal the sum of patients per protocol. In addition, 16 patients presented multiple cancer localizations, thus the total number of patients is less than the sum of patients per localization.

Table 3: Description of cancer localisations and administered fluoropyrimidine for the 513 patients included in the pharmacovigilance database

Administered FP	Cancer localization	Patient number per FP N (%)	Patient number per FP and localization N (%)
<b>5FU</b>		454 (88.5%)	
	Breast		167 (36.8%)
	Colon or rectum or rectosigmoid junction		120 (26.4%)
	Stomach or esophagus		63 (13.9%)
	Head and neck		49 (10.8%)
	Pancreas		26 (5.7%)
	Liver or biliary tract		7 (1.5%)
	Female genital tract other than ovary and fallopian tube		4 (0.9%)
Others		18 (4.0%)	
<b>Capecitabine</b>		38 (7.4%)	
	Colon or rectum or rectosigmoid junction		33 (86.8%)
	Breast		2 (5.3%)
	Stomach or esophagus		2 (5.3%)
Pancreas		1 (2.6%)	
<b>5FU and Capecitabine</b>		11 (2.1%)	
	Colon or rectum or rectosigmoid junction		8 (72.7%)
	Stomach or esophagus		2 (18.2%)
Liver or biliary tract		1 (9.1%)	
<b>UFT</b>		6 (1.2%)	
Colon or rectum or rectosigmoid junction		6 (100%)	
<b>5FU and UFT</b>		3 (0.6%)	
Colon or rectum or rectosigmoid junction		3 (100%)	
<b>Capecitabine and UFT</b>		1 (0.2%)	
Colon or rectum or rectosigmoid junction		1 (100%)	

Table 4: Pharmacovigilance study: Description of chemotherapy protocols in the 495 patients receiving FP from the beginning of treatment

<b>Standardized protocols</b>	<b>Number of patients (%)</b>
5FU or FUFA + platinum derivative	167 (33.7)
5FU + cyclophosphamide + anthracycline (FEC)	165 (33.3)
Capecitabine alone	39 (7.9)
5FU or FUFA + platinum derivative + taxane	38 (7.7)
5FU or FUFA + platinum derivative + targeted therapy	24 (4.9)
5FU or FUFA (LV5FU2 or Mayo regimen or other) alone	18 (3.6)
5FU or FUFA + irinotecan + platinum derivative	16 (3.2)
5FU or FUFA + irinotecan	8 (1.6)
UFT alone	6 (1.2)
5FU or FUFA + irinotecan + targeted therapy	5 (1.0)
5FU or FUFA + other chemotherapies	4 (0.8)
Capecitabine + platinum derivative + anthracycline	3 (0.6)
Capecitabine + taxane + targeted therapy	2 (0.4)

FUFA means 5FU associated with Folinic Acid.

Table 5: Number and typology of the 116 SAEs observed in 96 patients during the first two FP cycles

SAE typology	Number (%)	Involved FP (Number of SAE)	Chemotherapy protocol during the first two cycles		
			Chemotherapy protocol	Number of SAE at cycle 1	Number of SAE at cycle 2
Hematologic and/or lymphatic system disorder	62 (53.4)	5FU (58), UFT (1), capecitabine (2), 5FU and capecitabine (1)	All protocols	31	31
			5FU + cyclophosphamide + anthracycline (FEC)	10	7
			5FU or FUFA + platinum derivative	5	16
			5FU or FUFA + platinum derivative + taxane	5	3
			5FU or FUFA + platinum derivative + targeted therapy	5	2
			5FU or FUFA + irinotecan + platinum derivative	2	1
			Capecitabine alone	2	0
			5FU or FUFA + irinotecan	0	2
			5FU or FUFA + irinotecan + targeted therapy	1	0
			UFT	1	0
Nervous system disorder	8 (6.9)	5FU (8)	All protocols	5	3
			5FU or FUFA + platinum derivative	5	2
			5FU or FUFA + platinum derivative + targeted therapy	0	1
Gastro-intestinal disorder	15 (12.9)	5FU (13), UFT (1), capecitabine (1)	All protocols	7	8
			5FU or FUFA + platinum derivative	0	5
			5FU + cyclophosphamide + anthracycline (FEC)	2	1
			5FU or FUFA + platinum derivative + targeted therapy	2	0
			5FU or FUFA + irinotecan	1	1
			5FU or FUFA + irinotecan + platinum derivative	1	0
			UFT	1	0
			Capecitabine alone	0	1
Cutaneous disorder	6 (5.2)	5FU (5), capecitabine (1)	All protocols	4	2
			5FU + cyclophosphamide + anthracycline (FEC)	2	0
			5FU or FUFA + platinum derivative + targeted therapy	1	1
			Capecitabine alone	1	0
			5FU or FUFA + platinum derivative	0	1
General disorders	15 (12.9)	5FU (15)	All protocols	7	8
			5FU or FUFA + platinum derivative + taxane	4	2
			5FU or FUFA + platinum derivative + targeted therapy	2	2
			5FU or FUFA + platinum derivative	1	4
Immune system disorder	2 (1.7)	5FU (2)	5FU or FUFA + platinum derivative + targeted therapy	2	0
Renal and/or urinary tract disorder	3 (2.6)	5FU (3)	5FU or FUFA + platinum derivative + taxane	2	1
Cardiac disorder	4 (3.4)	5FU (2), capecitabine (2)	All protocols	3	1
			Capecitabine alone	2	0
			5FU or FUFA + platinum derivative + taxane	1	0
			5FU or FUFA + platinum derivative	0	1
Ear disorder	1 (0.9)	5FU (1)	5FU or FUFA + platinum derivative	0	1

Table 6: Description of SAEs leading to death, life-threatening prognosis or incapacity/disability (8 patients)

<b>Patient number</b>	<b>SAE outcome</b>	<b>Time of SAE (Cycle number)</b>	<b>SAE description</b>	<b>Chemotherapy protocol</b>
# 1	Patient death	2	Febrile neutropenia	5FU/carboplatin/cetuximab
# 2	Patient incapacity or disability	1	Peripheral neuropathy	5FU/oxaliplatin
# 3	Life-threatening prognosis	1	G3 mucositis + G3 thrombopenia + G3 neutropenia	5FU/docetaxel/cisplatin
# 4	Life-threatening prognosis	1	Myocardial infarction	Capecitabine
# 5	Life-threatening prognosis	1	Ischemic stroke	5FU/oxaliplatin
# 6	Life-threatening prognosis	1	Ischemic stroke	5FU/cisplatin
# 7	Life-threatening prognosis	2	Myocardial infarction	5FU/oxaliplatin
# 8	Life-threatening prognosis	3	Aggravation of renal failure	5FU/oxaliplatin

G means toxicity grade

Table 7: Standardized incidence rate (SIR)\* of various cancer locations in the Centre-Val de Loire area over the period 2007-2016

<b>Cancer localization</b>	<b>SIR [95% CI] in women</b>	<b>SIR [95% CI] in men</b>
All cancers	0.98 [0.96-1.00]	1.00 [0.99-1.02]
Head and neck	0.93 [0.89-0.98]	1.01 [0.97-1.04]
Breast	1.00 [0.98-1.02]	NA
Colon or rectum or rectosigmoid junction	0.97 [0.95-1.00]	1.03 [1.00-1.06]
Stomach	0.92 [0.87-0.97]	0.95 [0.90-0.99]
Oesophagus	0.93 [0.84-1.01]	1.02 [0.96-1.08]
Pancreas	0.98 [0.95-1.02]	0.99 [0.95-1.02]
Liver or biliary tract	NA	0.99 [0.94-1.04]

\*SIR is defined as the ratio between the number of estimated incident cases and the expected number of cases if the incidence rates in this geographical area were identical to those in metropolitan France (from the French National Institute of Cancer (INCa) - <https://www.e-cancer.fr/Expertises-et-publications/Catalogue-des-publications/Estimations-en-Centre-Val-de-Loire-d-incidence-et-de-mortalite-par-cancers-en-France-2007-2016>)

NA: Not available