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UPFRONT DPD DEFICIENCY DETECTION TO SECURE 5-FU ADMINISTRATION: PART 2- APPLICATION TO HEAD-AND-NECK CANCER PATIENTS

Manon Launay[1,2,3], **Joseph Ciccolini**[1,3,*], **Claire Fournel**[4], **Carmelo Blanquicett**[5], **Charlotte Dupuis**[4], **Nicolas Fakhry**[6], **Florence Duffaud**[4], **Sébastien Salas**[4], and **Bruno Lacarelle**[1,3]

[1]Laboratoire de Pharmacocinétique Clinique, La Timone University Hospital of Marseille, APHM Marseille France

[2]Laboratoire de Pharmacologie, European Hospital Georges Pompidou, APHP Paris France

[3]SMARTc Unit, Inserm S_911 CRO2, Aix Marseille Univ, Marseille France

[4]Medical Oncology Unit, La Timone University hospital of Marseille, APHM Marseille France

[5]Emory University School of Medicine and Atlanta VA Medical Center, USA

[6]Head-and-Neck Surgery Unit, La Conception University Hospital of Marseille, Marseille France

Abstract

Background—Upfront screening for dihydropyrimidine dehydrogenase (DPD) deficiency in patients scheduled for 5-FU should help reduce the risk of toxicities by preventive adaptive dosing. Our group has developed a simple functional testing categorizing patients upon their DPD status, i.e. extensive metabolizer (EM) or poor metabolizer (PM) patients, using UH2/U ratio measurement in plasma as a surrogate for DPD activity. 5-FU dosing can then be tailored according to DPD deficiency status.

Objectives—We present here an observational study of this strategy implemented in routine clinical practice when treating head-and-neck cancer patients.

Results—A total of 218 evaluable adult patients were treated with a 5-FU-regimen, with DPD-based adaptive dosing. Among them, 20 (9%) were identified as PM and received subsequently a 20–50% reduced dosing of 5-FU as compared with EM patients (2102 ±254 mg VS. 2577 ±353mg, $p<0.001$ ttest). Gender (Female) was associated with higher risk for being PM ($p=0.01$, Pearson's Chi squared test). Overall, early severe toxicities were seen only in 5% of patients, all being EM with standard dosing. Similarly, overall severe toxicities were observed in 12.8% of patients only, both figures being markedly lower than usually reported with standard 5-FU. Despite the average −20% reduction in 5-FU dosing between PM and EM patients, clinical efficacy was not statistically different between the two groups ($p = 0.2774$, chi-square test).

*Dr Joseph Ciccolini, SMARTc, Laboratoire de Pharmacocinétique Clinique, CHU Timone, 265 rue St Pierre, 13385 Marseille cedex 05, France., Tel.: +33 491 835 509, Fax: +33 491 835 667, joseph.ciccolini@univ-amu.fr.

CONFLICT OF INTEREST

The authors have to conflict of interest to disclose in relation with this work.

Conclusion—This study shows that 5-FU-related toxicities can be greatly reduced in routine clinical practice by the upfront detection of DPD deficient patients with simple adaptive dosing strategy.

Keywords

5-FluoroUracil; head and neck cancer; dihydropyrimidine dehydrogenase; adaptive dosing; DPD deficiency; efficacy; toxicity

1. INTRODUCTION

5-FU remains the backbone of several regimens to treat head-and-neck cancer patients – a disease with specifically frail patients often presenting with several co-morbidities impacting on drug disposition such as impaired liver or kidney functions. 5-FU itself is a drug whose handling is potentially hazardous because of a pharmacogenetic syndrome (a.k.a. DPD deficiency) leading to decreased ability to detoxify the drug in the liver (see “Upfront DPD Deficiency Detection To Secure 5-Fu Administration: Part 1- Where Do We Stand?” elsewhere in this issue). Several strategies can be undertaken to fix this problem, i.e. by upfront genotyping of the DPYD gene and search for relevant allelic variants predictive of severe toxicities, or by performing functional testing of the DPD enzyme [1, 2]. Regardless of the chosen option, preemptive checking for DPD status allows next to custom dosing of 5-FU, by cutting the dose according to the level of DPD deficiency. We have developed and implemented in routine clinical practice such DPD-based adaptive dosing of 5-FU at the University Hospital of Marseille. We present here the clinical data of such strategy in heavily treated routine head-and-neck cancer patients, both in terms of efficacy and safety, in a real-life setting.

2. MATERIALS AND METHOD

2.1. Patients and treatments

All head-and-neck cancer patients admitted to the Medical Oncology Unit of the La Timone University Hospital of Marseille, France, between January 2014 and July 2016, and scheduled for any 5-FU-based regimen, were considered. A total of 240 patients (61 F/179 M, mean age 60.7±9.9, range 30–84 years old) were first considered. All patients were treated following standard procedures of La Timone University Hospital of Marseille for treating head and neck cancers, including systematic pre-treatment screening for DPD deficiency using a phenotyping test. Cancer was localized on larynx, hypopharynx, oropharynx, nasopharynx, oral cavity or on other localizations. (see Table 1).

Among the 240 patients, 38 underwent surgery (15.8%), 11 had radiotherapy (4.6%), and 30 patients had radiochemotherapy (12.4%). Previous treatments were a former course of 5-FU (n=1; 0.4%), Cisplatin (n=6; 2.5%), Cetuximab (n=1; 0.4%), 5-FU+Cisplatin (n=2; 0.8%), 5-FU +Cisplatin +Carboplatin +Cetuximab (n=1; 0.4%), Cisplatin +Other chemotherapy (n=1; 0.4%), Carboplatin +Taxol (n=1; 0.4%), and Carboplatin +Other chemotherapy (n=1; 0.4%). Radiotherapy was associated on the DPD sampling day for 137 out of the 240 patients (57.1%) and concomitant treatments are described in Table 2.

2.2. DPD status determination

One 3 mL blood sample was withdrawn about 1 week before starting the treatment for DPD status evaluation as part of routine care in the Medical Oncology Unit of our institute. DPD deficiency was screened using a classic surrogate phenotyping test based upon the monitoring of the endogenous UH2 to U (UH2/U) ratio in plasma after standard solid–solid extraction using a simple and time-effective HPLC-UV method, adapted from the method previously described [3]. Calculation of such a ratio permits the determination of DPD status as a continuous variable. As for a previous study in digestive cancer patients [4], because no mathematical model was yet available, individuals were categorized as extensive metabolizers (EM, UH2/U>4) or poor metabolizers (PM, UH2/U<4) patients, this latter group being further divided in different subsets (i.e. simple reduced activity, mildly DPD deficient, intermediary DPD deficient, profoundly DPD deficient and completely DPD deficient, depending on their respective UH2/U ratio values).

2.3. 5-FU adaptive dosing

Doses were tailored prospectively according to the recorded DPD status with 15% to 100% dose reductions, using a simple and empirical geometric scale for cutting the dosing (the deeper the deficiency, the smaller the dose) already published [4]. Of note, further dose tailoring e.g., administration of the bolus) could be performed by the oncologist, regardless of the DPD status, depending on other clinical or paraclinical considerations such as comorbidities, age, co-medications, or any suspicion of a frail patient. (See Table 3)

2.4. Pharmacodynamic Endpoints

Toxicities (e.g., anemia, neutropenia, thrombopenia, mucositis, neuropathy, diarrhea, nausea) were monitored using standard CTCAE grading. Toxicities were evaluated as overall toxicities (i.e. mixing toxicities showing after the first courses and the delayed ones) and early severe toxicities (i.e., showing only after the first or the second course). Efficacy was evaluated using the standard RECIST criteria.

2.5. Statistical Analysis

Comparisons between groups were performed by running t-test and Pearson’s Chi-square test or Fisher’s exact test, depending on data distribution (R, version 3.1.3).

3. RESULTS

3.1. DPD determination and subsequent adaptive dosing

A total of 19 DPD phenotypes were not available, either because sample loss during routine care, absence of request for DPD screening during routine care or due to chromatographic interferences rendering the determination of the UH2/U ratio not precise enough to categorize precisely the patients to adapt 5-FU dosing next. Consequently, only 221 patients had DPD status evaluated. UH2/U ratios among those patients were not distributed following a normal law ($p < 0.0001$, Kolmogorov Smirnov testing). Twenty (i.e., 9%) out of the remaining 221 patients were categorized strictly as PM (Poor Metabolizers) requiring dose reduction and displayed mild (17 patients, i.e. 7.7%) or intermediary (3 patients, i.e.

1.4%) levels of DPD deficiency. No patient with profound or total deficiency was found. In addition, 34 patients (16%) presented with a reduced DPD activity (i.e., UH2/U comprised between 3 and 4) but this status did not lead to an automatic recommendation for dose tailoring. In this respect, they were not counted as PM patients here. Consequently, 201 patients were considered as EM. A difference in gender was observed between EM and PM patients (157M/44F vs. 10M/10F, p=0.01, Pearson's Chi-squared test) but no difference was observed in age (60.9±10.0 vs. 61.3±10.5 years, p=0.8639, t-test). As per French legislation, ethnicity could not be recorded in routine patients and therefore this parameter was not tested.

Forty EM patients out of 201 (i.e., 19.9%) had cut in dosing on 5-FU because of non-DPD-related suspicion of possible toxicities (e.g., frail patients, co-morbidities), 75% of them (n=30) through suppression of the initial bolus infusion. In the subset of EM patients, mean 5-FU total doses were 2577 ±353mg/m^2. In the PM subset (DPD deficient patients), 2 patients were excluded because dose adaptation was not confirmed. Therefore, PM patients with reduced dosing were n= 18 and statistical testing was performed on 218 patients. Mean reduction in dosing in PM patients was a 21% cut from standard dosing (range: −18% to −51%). Consequently, mean 5-FU total doses were 2102 ± 254 mg/m^2, i.e. −19% lower than EM patients. A statistical difference in dosing was evidenced between the two groups (p<0.0001, t-test).

3.2. Overal and early severe toxicities

Overall toxicity was not properly evaluated for one EM patient, therefore data from only 200 EM patients were available for studying this endpoint. A total of 28 out of 218 patients (12.8%) displayed severe toxicities, including 7 patients with grade-4 toxicities (3.2%). Severe toxicities were observed in 2 out of 18 PM patients (11%): one grade-3 nausea and one grade-3 mucitis. In the EM group, 26 out of 200 patients (13%) displayed severe toxicities: mucitis (12 patients, including one grade-4), anemia (5 patients, including 3 grade-4), nausea (6 patients, including one grade-4), thrombopenia (one patient), neutropenia (4 patients, including 2 grade-4) and diarrhea (one patient). One patient experienced 2 severe toxicities (anemia and mucitis) and one patient experienced 3 severe toxicities (neutropenia, thrombopenia and nausea). In terms of overall severe toxicities Pearson's chi-square testing found no statistical difference between the two subsets (p = 0.7875) (See table 4).

Regarding early severe toxicities, a total of 11 out of 218 patients (5%) displayed severe adverse-events after the first or the second administration of 5-FU, all of them being EM patients: anemia (3 patients, including 2 grade-4), neutropenia (3 patients, including 2 grade-4), mucitis (3 patients), diarrhea (1 patient) and nausea (1 patients). No PM patients with reduced dosing experienced early severe toxicities. Pearson's chi-square testing found a statistical difference between EM and PM patients (p = 0.0357) (See table 5).

3.3. Treatment efficacy

Patients with clinical benefit (CR + PR), stable disease and progressive disease in the EM subset were 40%, 5% and 43% respectively. Patients with clinical benefit (CR + PR), stable

disease and progressive disease in the PM subset were 56%, 11%, and 22% respectively. No statistical difference in response was found between the groups in terms of efficacy (p = 0.2774, Pearson's chi-square test) (See table 6).

4. DISCUSSION

Patients with DPD deficiency are prone to experience severe and sometimes deadly toxicities when treated with standard doses of 5-FU [2] or oral capecitabine [5]. Our group has developed a simplified method to establish, on a phenotyping basis, the DPD status prior to administrate fluoropyrimidine drugs. Upfront detection allows preventive cut in dosing, so as to prevent severe toxicities to show [6]. Determining the best strategy to sort patients on their DPD status is a long and still ongoing story (refer to "Upfront DPD Deficiency Detection to secure 5-Fu Administration: Part 1- Where Do We Stand?" elsewhere in this issue). In our institute, we have adapted and implemented in routine clinical practice a functional approach allowing next DPD-based adaptive dosing to be performed, using a simplified geometric scale to tailor 5-FU dosing. We previously showed in digestive oncology that implementing this strategy led to improving the efficacy/toxicity balance in patients treated with any 5-FU containing regimen [4]. Previously, we had published a case-control study with head-and-neck cancer patients showing that incidence of severe toxicities was sharply reduced from 22 to 9% by upfront DPD testing and subsequent adaptive dosing [3]. Here, we present the performance of this strategy in routine clinical setting in head-and-neck cancer patients. As a real-life observational study, all head and neck patients treated in the Medical Oncology unit of La Timone university hospital of Marseille France were considered, provided that they were scheduled for any 5-FU-based regimen, regardless of tumor localization, staging, or associated treatments. The resulting variety of settings can be seen as major confounding factors. However, we deliberately chose to not sub-categorize the patients (e.g., analyzing separately chemotherapy and chemotherapy + radiotherapy patients), to evaluate the global performance of our strategy in the most harsh conditions. Almost 10% of the patients were categorized as PM, i.e. showing signs for impaired DPD activity per UH2/U ratio measurement: 3 patients (1.4%) with intermediary deficiency (UH2/U comprised between 1 and 2) and 17 patients (7.7%) with mild deficiency (UH2/U comprised between 2 and 3). Here, no patients with profound or total DPD deficiency (i.e., UH2/U values below 1) were identified over the observation period. In addition, 16% of patients were identified with signs for reduced DPD activity (3<UH2/U<4), but this grey-zone category is considered in our institute as in-between patients for whom we cannot recommend systematically a reduction in 5-FU dosing. Overall, we observed therefore a total of 25% of patients with some kind of abnormality on DPD function, even if only 35% of them (i.e., 9% in total) led to recommending an actual cut in dosing – a value consistent with the previous figures we reported using phenotyping testing [3,4]. This value is markedly higher than the incidence of DPD deficiency usually detected by genotyping DPYD [1], but this difference in the incidence of DPD-deficiency depending on the screening method has been already reported before [3, 4]. Of note, gender (F) was associated with reduced DPD activity, an observation fully in line with previous studies published in other settings [7–11]. Conversely, age was not associated with PM status because of the 15 patients of 75 years old or above, only one was PM, an observation consistent again with

previous reports showing that 5-FU clearance is not influenced by age [7]. An average 21% cut in 5-FU dosing was performed in the PM patients, using the geometric scale previously published [4]. Consequently, mean doses administered in PM patients were 19% lower than mean doses in EM patients. Of note, this difference was slightly smaller than the initial reduction (21%) from standard dose because several EM patients had a cut in dosing as well, i.e. bolus was not administered. Because of the real-life setting, empirical dose adjustments were frequent indeed due to a variety of clinical considerations and thus had to be taken into account in this study, to test the robustness of our strategy. Overall, 12.8% of severe toxicities were registered, a value markedly lower than previously published data regarding the safety of 5-FU-based therapy with or without radiotherapy in head-and-neck cancer, i.e. 25%–50%, including frequent cases of febrile neutropenia [12–14]. Of note, it is not possible to attribute the 12.8% remaining toxic events to a specific drug, including 5-FU, because patients were all treated with multiple therapies associating mostly platinum derivatives, or paclitaxel, with possible combined effects in terms of cumulative toxicities. Here, all toxicities, i.e. including delayed or cumulative side-effects, were recorded, and not only the early ones showing after the first or the second course of chemotherapy as with most studies investigating on DPYD genetic polymorphisms. However, no difference in severe toxicities was found between PM and EM patient, thus demonstrating that DPD deficiency is not anymore a major risk of triggering life-threatening toxicities, provided that preventive dose reduction is undertaken. Seven EM patients treated with standard 5-FU displayed grade-4 hematological toxicities, however no sepsis was observed. No particular co-morbidities or specific covariate (age, gender, weight, BSA) could be identified as culprit for these cases (data not shown). When focusing on early toxicities only (i.e., those showing after the first of the second course of 5-FU administration), only 5% of such severe side effects were recorded, a value close to the one we previously published in a case-control study [3]. Interestingly, not loss in efficacy was observed in PM patients with reduced dosing. Despite the lack of therapeutic drug monitoring, we can hypothesize that specifically cutting 5-FU dose in patients with impaired DPD ensures non-toxic drug levels to be sustained, as for standard dosing administered in patients with no DPD deficiency. In this respect, it is not surprising that efficacy was not hindered by our tailored dosing, whereas tolerance was improved. The strategy we have implemented in routine is certainly not optimal, since it relies on a fairly complicated HPLC-UV analysis because UH2 is best quantified at 210 nm, a non-specific wavelength. Consequently, UH2/U ratio determination can be difficult, and in this study, 19 samples (7.8%) could not be analyzed, partly because of chromatographic interferences. Also, the fact that our patients were all undergoing combinational therapies prevents us to associate unequivocally our PD endpoints with 5-FU only. Furthermore, unlike genotyping DPYD, there is little data made available to assess the sensitivity and the specificity of DPD functional testing as a mean to detect patients at risk of severe toxicities upon fluoropyrimidines administration. Consequently, most groups advocate for implementing genotyping DPYD as the primary strategy to avoid 5-FU-related toxicities [15–17], rather than phenotyping as we did. In a previous retrospective study, we showed that ratio determination permitted to detect 70% of the severe toxicities and 80% of the toxic death in patients treated with either 5-FU or capecitabine, but this study was not designed to evaluate specificity and its retrospective nature failed to meet appropriate level of evidence. Despite this, and based upon several clinical reports or case-reports in our

institute, it has been decided to implement this technique in routine, and real-life data suggest today that the efficacy/toxicity balance of 5-FU can be improved indeed, including in heavily treated head-and-neck cancer patients with several co-morbidities and no limit in age. Of note, 15 patients were 75 years or older (i.e., 14 EM, 1 PM), including 4 older than 80 years and none of them displayed severe toxicities. Despite the previously mentioned drawbacks, functional testing remains an active field of investigation and improved methods are regularly published [18, 19]. Of note, the ESMO has recently issued its recommendations for treating colorectal cancer, and this panel has chosen to not recommend upfront DPD screening, because of the poor sensitivity of genotyping approaches, and the lack of consensus on functional testing [20]. This recent position has fueled several harsh controversies among specialists [21, 22]. Here, our clinical observational study suggests indeed that 5-FU-induced toxicities are not a fatality, even in DPD-deficient patients, provided that adequate dose tailoring is performed.

CONCLUSION

This observational study performed on 218 fully evaluable patients with head–and-neck cancer shows that it is possible to implement upfront DPD screening in routine clinical practice to reduce the risk of 5-FU-induced toxicities. Our clinical observation shows that the global incidence of severe adverse events (12.7%) is lower than the figures usually published in head and neck cancer, and that reducing 5-FU dosing in PM patients does not affect treatment efficacy. Despite the limitations related to its monocentric nature and the absence of control arm, this observational study advocates for pursuing current efforts to systematize pre-emptive DPD screening for securing 5-FU-based regimen in oncology.

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Table 1

Cancer localizations for the 240 patients

Cancer localisation	n	%
Larynx	46	19.2
Hypopharynx	27	11.3
Oropharynx	22	9.2
Nasopharynx	28	11.7
Oral cavity	86	35.9
Other localization	30	12.5
Larynx/Hypopharynx/Oropharynx/Nasopharynx	1	0.4

Table 2

Concomitant treatment administered with 5-FU.

Associated treatment	n	%
Cetuximab + Cisplatin	34	14.2
Cetuximab + Carboplatin	17	7.1
Cisplatin	106	44.2
Cisplatin + Taxol	50	20.8
Carboplatin	26	10.8
Other regimen (Gemcitabine, Dacarbazine, Cetuximab, Cisplatin, Carboplatin)	6	2.5
Not reported	1	0.4

Table 3

DPD status category according to UH_2/U ratio value and subsequent dose tailoring.

DPD status		UH/U ratio	Theoretical adaptative dosing
Extensive metabolizers (EM)		> 4	Standard 5-FU dosing
Poor metabolizers (PM)	*Grey-zone patients*	[3 – 4]	Alert for reduced activity, without systematic dose reduction
	mildly DPD deficient	]2 – 3[	20% dose reduction
	intermediary DPD deficient	]1 – 2]	30% dose reduction
	profoundly DPD deficient	]0.5 – 1]	50% dose reduction
	completely DPD deficient	< 0.5 or UH2 not detectable upon HPLC analysis	5-FU precluded

Table 4

Toxicities in the EM and PM subsets (*: 1 patient had report on toxicity not available, **: 2 patients were excluded because dose adaptation was not confirmed)

	EM (200 patients*)		PM (18 patients**)		*p-value*
	n	*%*	**n**	*%*	
No toxicity	62	*31*	7	*39*	*p =0.7875 (Pearson's chi-square test)*
G1-G2 toxicities	112	*56*	9	*50*	
Severe toxicities	26	*13*	2	*11*	

Table 5

Early toxicities in the EM and PM subsets (*: 3 patients had report on early toxicity not available, **: 2 patients were excluded because dose adaptation was not confirmed)

	EM (198 patients*)		PM (18 patients**)		*p-value*
	n	*%*	**n**	*%*	
No toxicity	63	*32*	11	*61*	*p = 0.0357 (Pearson's chi-square test)*
G1-G2 toxicities	124	*63*	7	*39*	
Severe toxicities	11	*6*	0	*0*	

Table 6

Clinical responses in the EM and PM subsets (**2 patients excluded because dose adaptation was not confirmed)

	EM (201 patients)		PM (18 patients**)		*p-value*
	n	*%*	**n**	*%*	
Stable disease	10	*5*	2	*11*	*p = 0.2774 (Pearson's chi-square test)*
Clinical benefit	80	*40*	10	*56*	
Progressive disease	86	*43*	4	*22*	
NA	25	*12*	2	*11*	

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