The Oncologist®

Cancer Diagnostics and Molecular Pathology

Implementing *DPYD*2A* Genotyping in Clinical Practice: The Quebec, Canada, Experience

Catherine Jolivet,[a] Rami Nassabein,[a] Denis Soulières,[a] Xiaoduan Weng,[a] Carl Amireault,[b] Jean-Pierre Ayoub,[a] Patrice Beauregard,[c] Normand Blais,[a] Christian Carrier,[d] Alexis-Simon Cloutier,[b] Alexandra Desnoyers,[c] Anne-Sophie Lemay,[d] Frédéric Lemay,[c] Rasmy Loungnarath,[a] Jacques Jolivet,[e] François Letendre,[f] Mustapha Tehfé,[a] Charles Vadnais,[a] Daniel Viens,[g] Francine Aubin[a]

[a]Centre Hospitalier de l'Université de Montréal (CHUM), Montreal, Quebec, Canada; [b]Hôpital Pierre-Boucher, Longueuil, Quebec, Canada; [c]Centre Hospitalier de l'Université Sherbrooke, Sherbrooke, Quebec, Canada; [d]Centre Hospitalier Régional Trois-Rivières, Trois-Rivières, Quebec, Canada; [e]Centre Intégré de Santé et de Services Sociaux (CISSS) des Laurentides, Saint-Jérôme, Quebec, Canada; [f]CISSS Montérégie Ouest, Châteauguay, Quebec, Canada; [g]Hôpital Sainte-Croix, Drummondville, Quebec, Canada

Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Fluoropyrimidines toxicity • *DPYD* genotyping • *DPYD*2A* • Fluorouracil • Capecitabine

Abstract

Background. Fluoropyrimidines are used in chemotherapy combinations for multiple cancers. Deficient dihydropyrimidine dehydrogenase activity can lead to severe life-threatening toxicities. *DPYD*2A* polymorphism is one of the most studied variants. The study objective was to document the impact of implementing this test in routine clinical practice.

Methods. We retrospectively performed chart reviews of all patients who tested positive for a heterozygous or homozygous *DPYD*2A* mutation in samples obtained from patients throughout the province of Quebec, Canada.

Results. During a period of 17 months, 2,617 patients were tested: 25 patients tested positive. All were White. Twenty-four of the 25 patients were heterozygous (0.92%), and one was homozygous (0.038%). Data were available for 20 patients: 15 were tested upfront, whereas five were identified after severe toxicities. Of the five patients confirmed after toxicities, all had grade 4 cytopenias, 80% grade ≥3 mucositis, 20% grade 3 rash, and 20% grade 3 diarrhea. Eight patients identified with *DPYD*2A* mutation prior to treatment received fluoropyrimidine-based chemotherapy at reduced initial doses. The average fluoropyrimidine dose intensity during chemotherapy was 50%. No grade ≥3 toxicities were observed. *DPYD*2A* test results were available in an average of 6 days, causing no significant delays in treatment initiation.

Conclusion. Upfront genotyping before fluoropyrimidine-based treatment is feasible in clinical practice and can prevent severe toxicities and hospitalizations without delaying treatment initiation. The administration of chemotherapy at reduced doses appears to be safe in patients heterozygous for *DPYD*2A*. ***The Oncologist*** 2021;26:e597–e602

Implications for Practice: Fluoropyrimidines are part of chemotherapy combinations for multiple cancers. Deficient dihydropyrimidine dehydrogenase activity can lead to severe life-threatening toxicities. This retrospective analysis demonstrates that upfront genotyping of *DPYD* before fluoropyrimidine-based treatment is feasible in clinical practice and can prevent severe toxicities and hospitalizations without delaying treatment initiation. This approach was reported previously, but insufficient data concerning its application in real practice are available. This is likely the first reported experience of systematic *DPYD* genotyping all over Canada and North America as well.

Introduction

5-Fluorouracil (5-FU) and capecitabine are part of combination chemotherapy protocols for the treatment of various cancers, especially gastrointestinal (GI), breast, and squamous cell carcinoma of the head and neck (HNSCC) [1]. These two fluoropyrimidines may cause GI, hematological, and cutaneous toxicities. About 10% of patients experience

Correspondence: Francine Aubin, M.D., Centre Hospitalier de l'Université de Montréal (CHUM), 1000 Rue St-Denis, Monteal, Quebec, Canada, H2X 0C1. Telephone: 1-514-890-8000 ext. 20688; e-mail: francine.aubin.chum@ssss.gouv.qc.ca Received August 7, 2020; accepted for publication November 20, 2020; published Online First on December 23, 2020. http://dx.doi.org/10.1002/onco.13626

grade 3 or 4 toxicities that lead to dose interruption or discontinuation and may necessitate hospitalization [2]. These toxicities also have an impact on patients' quality of life and health care resources. Moreover, lethal toxicities have been reported in 0.5% to 1% of patients [3].

5-FU is converted intracellularly to active metabolites, which inhibit thymidylate synthase and interfere with RNA and DNA synthesis, leading to cell death [1]. Dihydropyrimidine dehydrogenase (DPD), a rate-limiting enzyme encoded by the *DPYD* gene, is responsible for pyrimidine catabolism and hepatic 5-FU catabolism [1]. DPD deficiency leads to decreased 5-FU clearance and enhanced toxicity (Fig. 1). Genetic polymorphism in *DPYD* can result in a complete or partial loss of DPD enzymatic activity. Up to 128 *DPYD* genetic variants have been reported with mixed effect on enzymatic activity. Four have been identified as clinically significant to predict toxicities: *DPYD*2A* (c.1905+1G>A), *DPYD*13*(c.1679T>G), *DPYD*9B* (c.2846A>T), and HapB3 (c.1129–5923C>G) [4–10]. Heterozygote and homozygote *DPYD*2A* mutations have been identified in up to 1% and 0.1% of White populations, respectively [11]. This mutation was found to be responsible for 5% of grade 3–4 fluoropyrimidines toxicities, especially prolonged neutropenia and mucositis, and can sometime lead to treatment related mortality [12].

In a prospective clinical trial, upfront *DPYD*2A* testing with subsequent dose modifications was shown to reduce grade ≥3 toxicities compared with historical controls. On a population level, the upfront genotyping also seemed cost-saving [11]. However, preemptive *DPYD* testing has not been widely adopted. Concerns exist regarding the impact of dose modifications on treatment efficacy, the feasibility of implementing the test in clinical practice without treatment delays, and cost-effectiveness. As *DPYD*2A* genotyping became available in our center (Centre Hospitalier de l'Université de Montréal [CHUM]), we aimed to review our experience in Quebec province, Canada, since its introduction in March 2017.

Materials and Methods

Genomic DNA was extracted from peripheral blood mononuclear cells using the Qiasymphony system (Qiagen Inc., Germantown, MD). Variant alleles of *DPYD*2A* (c.1905+1G>A, IVS14+1G>A, rs3918290) were screened by real-time polymerase chain reaction with TaqMan probes (Thermo Fisher Scientific, Waltham, MA). Positive control heterozygote variant allele DNA was kindly provided by Dr. Schellens from Netherlands Cancer Institute, Utrecht University, The Netherlands [11]. Our essay was validated internally and externally and approved for clinical use by the Institut National D'Excellence en Santé et Services Sociaux (INESSS) in February 2017. At the time of this analysis, our institution, CHUM was the only center testing for *DPYD*2A* mutation in the province of Quebec, Canada. The test is performed twice weekly with a cost of CAD $18.30 per analysis.

Patients aged ≥18 years who tested positive for a heterozygote or homozygote mutation since the implementation of the test in March 2017 were identified. Data were either collected on site or through questionnaires sent to the treating physician in other institutions. Medical charts were reviewed for multiple variables, including demographic characteristics (age, gender, ethnicity), cancer type and stage, planned fluoropyrimidine-based treatment, and toxicities after exposure to fluoropyrimidine-based therapy. DPD-deficient patient toxicities were reviewed and graded according to the Common Terminology Criteria for Adverse Events version 5.0 [13].

The average test response time and treatment delays related to the test were also examined. Results were analyzed by descriptive statistics.

The study was approved by the CHUM research ethics board.

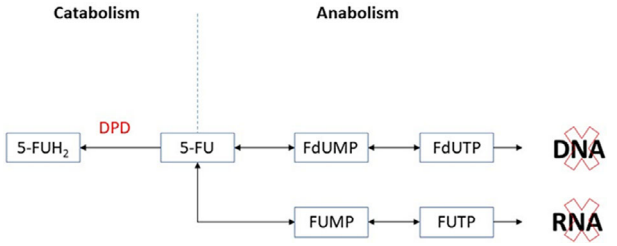

Figure 1. Role of DPD in irreversibly metabolizing 5-flurouracil (5-FU) to an inactive metabolite (5-FUH_2). On the right, active metabolites of 5-FU—fluorouridine monophosphate, fluorodeoxyuridine monophosphate, fluorouridine triphosphate, and fluorodeoxyuridine triphosphate—incorporate into DNA and RNA and lead to inhibition of cell replication [27].
Abbreviations: 5-FU, 5-fluorouracil; 5-FUH_2, 5,6-dihydro-5-fluorouracil; DPD, dihydropyrimidine dehydrogenase; FdUMP, fluorodeoxyuridine monophosphate; FdUTP, fluorodeoxyuridine triphosphate; FUMP, fluorouridine monophosphate; FUTP, fluorouridine triphosphate.

Results

From March 2017 to August 2018, 2,617 *DPYD*2A* genotyping assays were performed, of which 81% were referred from 72 different hospitals in the province. Twenty-five patients were found to harbor a mutation, of whom all were White; 75% male and 25% female. Twenty-four of the 25 patients were heterozygous (0.92%), and one was homozygous (0.038%).

*DPYD*2A* genotype testing results were available in an average of 6 days (including transport between institutions), causing no significant delays in treatment initiation according to 99% of queried physicians. Data and variables for analysis were available for 20 of the 25 patients: 15 had GI tumors, two had breast cancer, and two had HNSCC. One patient did not have cancer but was tested as her son had been identified as a heterozygous *DPYD*2A* mutation carrier. *DPYD*2A* genotype testing was performed upfront, before chemotherapy, in 14 patients. In five patients, it was performed after severe toxicities encountered during fluoropyrimidine-based chemotherapy.

Of the five patients with mutations identified after toxicities, all had grade 4 neutropenias, four had grade ≥3 mucositis, two had grade 4 thrombocytopenia, one had grade 3 desquamating generalized rash, and one had grade 3 diarrhea. All had experienced toxicities after the first treatment cycle administered at full 5-FU dose. Average duration of hospitalization because of febrile neutropenia

Table 1. *DPYD*2A* heterozygous patients identified after 5-FU severe toxicities

Age, yr	Gender	Cancer type	Stage	Chemotherapy received	Toxicities	Hospitalization for treatment of AEs, days	Subsequent treatment
64	Male	Rectal	IV	FOLFIRI	Grade 4 neutropenia Grade 4 thrombocytopenia Grade 3 mucositis	13	Raltitrexed
53	Male	Anal	III	5-FU + mitomycin + RT	Grade 4 neutropenia Grade 3 mucositis	20	RT alone[a]
42	Male	Gastric	IV	FOLFOX	Grade 4 neutropenia Grade 4 thrombocytopenia Grade 3 mucositis requiring TPN Grade 3 generalized desquamative rash	17	Paclitaxel and ramucirumab
56	Male	Anal	Localized disease[b]	5-FU + mitomycin + RT	Grade 4 neutropenia Grade 3 mucositis	14	Cisplatin and RT
69	Female	Colon	III	FOLFOX	Grade 4 neutropenia Grade 3 diarrhea Grade 3 alopecia (complete hair loss)	13	TOMOX

Abbreviations: 5-FU, 5-fluorouracil; AE, adverse event; FOLFIRI, irinotecan, leucovorin, and 5-FU; FOLFOX, oxaliplatin, leucovorin, and 5-FU; RT, radiation therapy; TOMOX, raltitrexed and oxaliplatin; TPN, total parenteral nutrition.
[a]Performance status not admissible to further chemotherapy treatment after toxicities.
[b]Exact TNM staging not available. All toxicities were reported according to the Common Terminology Criteria for Adverse Events version 5.0 [13].

Table 2. *DPYD*2A*-mutated patients treated alternatively

Age, yr	Gender	Cancer type	Stage	Original treatment choice	*DPYD*2A* mutation	Post-testing treatment
57	Male	Head and neck	III	Carboplatin, 5-FU, and RT	Heterozygous	Cisplatin + RT
66	Female	Breast	IV	Capecitabine	Heterozygous	Carboplatin and gemcitabine
31	Female	Breast	II	Capecitabine	Heterozygous	Anastrozole + goserelin
62	Male	Head and neck	III	Carboplatin, 5-FU, and RT	Heterozygous	Cisplatin + RT
56	Male	Pancreas	IV	FOLFIRINOX	Homozygous	Gemcitabine and nab-paclitaxel

Abbreviations: 5-FU, 5-fluorouracil; FOLFIRINOX, oxaliplatin, irinotecan, leucovorin, and 5-fluorouracil; RT, radiation therapy.

Table 3. Fluoropyrimidine-based regimens in *DPYD*2A* heterozygous patients

Age, yr	Gender	Cancer type	Stage	Chemotherapy regimen	Initial→ maximal 5-FU dose, %	Maximum tolerated 5-FU dose, %	Grade 3 or 4 adverse events
61	Male	Colon	III	FOLFOX	50 → 87	75	None
55	Male	Gastro-esophageal junction	IV	Cisplatin, 5-FU, and trastuzumab	25 → 50	50	None
70	Male	Rectal	III	Capecitabine	33 → **100**	66	None
65	Male	Colon	IV	FOLFOX	25 → 50	50	None
60	Male	Rectal	IV	FOLFOX and bevacizumab	50 → 50	50	None
74	Male	Colon	III	FOLFOX (adjuvant)	50 → 50	50	None
28	Male	Colon	IV	FOLFOX (adjuvant)	50 → 50	50	None
48	Female	Colon	IV	FOLFOX	50 → **100**	87	None

Abbreviations: 5-FU, 5-fluorouracil; FOLFOX, oxaliplatin, leucovorin, and 5-FU.

was 15 days. In addition, one patient required total parenteral nutrition because of severe mucositis. None of these five patients received any further treatment with fluoropyrimidine-based chemotherapy. One patient with localized anal cancer had prolonged clinical deterioration after toxicities that rendered him ineligible for further chemotherapy. Table 1 outlines second-line treatments administered after severe 5-FU toxicities.

Of patients screened for *DPYD*2A* mutations before starting fluoropyrimidine-based chemotherapy, five were allocated to a different type of chemotherapy (Table 2). One patient refused treatment. This patient was a 74-year-old

man with stage IV gastrointestinal cancer, for which a palliative approach was chosen. Eight patients received fluoropyrimidine-based chemotherapy at 25% to 50% reduced initial doses (Table 3). The average maintained dose reduction was 50% throughout treatment. Some patients received higher subsequent doses after well-tolerated initial treatment cycles, and two patients reached full fluoropyrimidine doses. Both patients required subsequent dose reductions to 66% and 87% after grade 2 diarrhea and grade 2 mucositis. No grade ≥3 toxicities were observed in patients with *DPYD*2A* mutation identified upfront. No patient with preemptive dose reductions stopped treatment because of toxicity. One patient completed 12 cycles of adjuvant FOLFOX (oxaliplatin, leucovorin, and 5-FU) administered at 50% of the dose. Another patient completed concomitant chemoradiation for rectal cancer with 5-FU dose escalations up to 100% and subsequent dose de-escalations to 66%. One patient received up to 14 cycles of dose-reduced FOLFIRI (irinotecan, leucovorin, and 5-FU) in combination with bevacizumab.

Two patients had previous fluoropyrimidines exposures. One patient had received one cycle of FEC (5-FU, epirubicin, and cyclophosphamide) as adjuvant treatment for breast cancer and experienced grade 4 neutropenia, prompting a treatment change. In our study, this patient was identified preemptively and treated with carboplatin and gemcitabine instead of capecitabine. The other patient had received concomitant 5-FU and radiation therapy for localized rectal cancer. A dose reduction to 75% had been needed because of significant asthenia, but full treatment had been completed without significant toxicities. Treatment was changed to raltitrexed for recurrent metastatic disease after *DPYD*2A* mutation identification.

Discussion

In this retrospective analysis, the prevalence in our population was 0.92% and 0.038% for heterozygote and homozygote *DPYD*2A* mutations, respectively. It should be noted that the majority of tested patients were White. This is comparable to published data by Deenen et al. [11]. The prevalence described in our study is, however, probably overestimated because some heterozygous variants were retrospectively identified after major fluoropyrimidine-related toxicities.

In our cohort, five patients were found to have *DPYD*2A* mutations after fluoropyrimidine-related toxicities that led to treatment interruptions and hospitalizations. Resulting deterioration of performance status and treatment delays after fluoropyrimidine toxicities may lead to disease progression and affect survival outcomes. All patients experienced febrile neutropenia, and 80% had mucositis, consistent with toxicities described as the most likely experienced with *DPYD*2A* genotype according to a pooled analysis of data [7]. Patients treated without upfront *DPYD* testing and carried *DPYD*2A* variants had severe toxicities after the first treatment cycle. These severe adverse effects could have been avoided with preemptive *DPYD*2A* mutation testing. Management of these symptoms and toxicities is also expensive. Test cost is low (CAD $18.30) and readily accessible for patients throughout Quebec province, and the results are available in an average of 6 days. Initial concerns about response time and treatment delays were not validated. During the period of data collection for this study, 2,617 tests were performed for an approximate total cost of CAD $47,890. One day of hospitalization in the province of Quebec costs at least CAD $1,000. Assuming that each of the five patients identified with *DPYD* mutations had an average of 15-day hospitalizations, cost estimates suggests that upfront identification is potentially cost-saving, as already demonstrated by Deenen and colleagues [11].

Our analysis shows that all patients found upfront to have *DPYD*2A* mutations did not experience severe toxicity after preemptive fluoropyrimidine dose reductions. In a prospective trial, Deenen et al. demonstrated that 50% fluoropyrimidine dose reduction in *DPYD*2A* heterozygote variants resulted in 45% reductions in grade ≥ 3 toxicity with no deaths [11]. Dose adjustments performed by Hendricks et al. in a prospective trial showed a decrease of the relative risk for severe fluoropyrimidine-related toxicity by 1.31 using genotype-guided dosing compared with 2.87 in an historical cohort of *DPYD*2A* carriers. This reduction was also seen in other *DPYD* variants included in the trial [14]. However, not all *DPYD* mutation carriers experience severe toxicity. Thus, dose escalation should be adopted to ensure that maximal tolerated dose is administered. Future studies should focus on evaluating treatment response and survival outcomes in *DPYD*2A* carriers treated with reduced fluoropyrimidine doses to confirm equivalent therapeutic results. This is particularly important in gastrointestinal cancers in which alternative treatments to 5-FU or capecitabine are limited. In metastatic colorectal cancer, some studies have suggested that raltitrexed is an adequate therapeutic alternative to 5-FU [15, 16]. Nevertheless, there are no studies demonstrating equivalent efficiency of TAS-102 or raltitrexed in the adjuvant setting. Alternative treatment options, however, are available for cancers of other sites. As observed in our study, patients with head and neck cancer can be treated effectively with cisplatin-based chemoradiotherapy, and patients with breast cancer can be treated with an array of other molecules.

Our study was conducted in Quebec province, Canada, within regional hospitals and academic centers, demonstrating the feasibility of implementing upfront *DPYD*2A* screening in clinical practice. *DPYD* genotyping is a highly sensitive, specific, and rapid technique, but it is important to remember that it does not detect all variants and therefore cannot prevent all toxicities. *DPYD*2A* mutation is associated with significant decrease in the DPD enzyme activity. Other *DPYD* variants have different prevalence in other populations and variable impact on enzyme activity, as some can cause only 25% decrease, associated with variable toxicity profile [17]. Combined, detection rate might increase, and further toxicities can be prevented. Henricks et al. published a prospective safety analysis with individualized *DPYD* genotype-guided dosage including four *DPYD* variants: *DPYD*2A*, c.2846A>T, c.1679T>G, and c.1236G>A. Eight percent of patients were found to be heterozygous carriers, leading to a decrease in fluoropyrimidines related toxicities in a larger population [14]. Henceforth, our institution has now instituted, since July 2019, upfront screening for these four *DPYD*

genotypes. Since implementation of the four variants testing, we identified 5% of heterozygous carriers in our population. A cost analysis done by Henricks et al. showed that the screening strategy is not expected to yield additional costs [18].

Several trials assessed the feasibility of DPD phenotyping using different methods, either by measuring the DPD enzyme activity in peripheral blood mononuclear cells or by measuring the uracil or its metabolite dihydrouracil concentrations in plasma or urine [17, 19, 20]. It should be noted that despite the high sensitivity of the DPD enzymatic activity method to detect all cases of enzyme deficiency, it is technically delicate, and interpretation requires the determination and the validation of threshold values of enzyme activity to distinguish DPD-deficient patients from normal ones. Thus, there is no established consensus for an optimal assay. Fluoropyrimidine dose reduction recommendation of each genotype is individualized based on linking *DPYD* genotype with variability in DPD enzyme activity and toxicities observed, which is known as the gene activity score.

The American Society of Clinical Oncology does not endorse *DPYD* genotyping but mentions the risk of severe toxicity and 1% of mortality while discussing chemotherapy options [21]. There are no specific National Comprehensive Cancer Network recommendations. The U.S Food and Drug Administration states a warning in the 5-FU monograph about the possibility of toxicity in some patients who may carry DPD enzyme genetic variants [22]. The European Society for Medical Oncology guidelines for colorectal cancer management, last updated in 2016, mention the option of DPD testing prior to fluoropyrimidine administration [23]. Since April 2020, the European Medicines Agency has recommended that patients should be tested for the lack of enzyme DPD before starting cancer treatment with fluorouracil or with the related medicines, capecitabine, and tegafur [24].

INESSS is one of the first governmental institutions to encourage physicians to discuss with its patients the risk of 5-FU or capecitabine toxicity based on genetic mutations and recommend upfront *DPYD* genotyping with proper dose modifications according to the variant identified [25]. Recently published in 2018, the French Clinical Oncologic Pharmacology group (Groupe de Pharmacologie Clinique Oncologique–Unicancer) and Hospital Pharmacogenetic National Network (Réseau national de pharmacogénétique hospitalière) recommend the screening of DPD deficiency before initiating chemotherapy containing 5-FU or capecitabine with DPD phenotyping and *DPYD* genotyping. They also advise to reduce 5-FU dosing according to DPD status with the intention to increase the dose to the maximum tolerated in the curative settings [26].

Conclusion

In summary, upfront genotyping before fluoropyrimidine-based treatment is feasible in clinical practice and may prevent severe toxicities and hospitalizations without delaying treatment initiation. The administration of chemotherapy at adjusted doses appears to be safe in *DPYD*2A* heterozygous patients. Our study adds to the previous prospective and retrospective trials supporting upfront *DPYD* genotyping and dose individualization to improve safety in patients receiving fluoropyrimidine-based chemotherapy.

Author Contributions

Conception/design: Catherine Jolivet, Denis Soulières, Francine Aubin

Provision of study material or patients: Catherine Jolivet, Denis Soulières, Xiaoduan Weng, Carl Amireault, Jean-Pierre Ayoub, Patrice Beauregard, Normand Blais, Christian Carrier, Alexis-Simon Cloutier, Alexandra Desnoyers, Anne-Sophie Lemay, Frédéric Lemay, Rasmy Loungnarath, Jacques Jolivet, François Letendre, Mustapha Tehfé, Charles Vadnais, Daniel Viens, Francine Aubin

Collection and/or assembly of data: Catherine Jolivet, Denis Soulières, Xiaoduan Weng, Carl Amireault, Jean-Pierre Ayoub, Patrice Beauregard, Normand Blais, Christian Carrier, Alexis-Simon Cloutier, Alexandra Desnoyers, Anne-Sophie Lemay, Frédéric Lemay, Rasmy Loungnarath, Jacques Jolivet, François Letendre, Mustapha Tehfé, Daniel Viens, Charles Vadnais, Francine Aubin

Data analysis and interpretation: Catherine Jolivet, Rami Nassabein, Denis Soulières, Xiaoduan Weng, Charles Vadnais, Francine Aubin

Manuscript writing: Catherine Jolivet, Rami Nassabein, Denis Soulières, Francine Aubin

Final approval of manuscript: Catherine Jolivet, Rami Nassabein, Denis Soulières, Xiaoduan Weng, Carl Amireault, Jean-Pierre Ayoub, Patrice Beauregard, Normand Blais, Christian Carrier, Alexis-Simon Cloutier, Alexandra Desnoyers, Anne-Sophie Lemay, Frédéric Lemay, Rasmy Loungnarath, Jacques Jolivet, François Letendre, Mustapha Tehfé, Charles Vadnais, Daniel Viens, Francine Aubin

Disclosures

Denis Soulières: Merck, Pfiizer, Bristol-Myers Squibb, Eisai, Ipsen (SAB), Merck, Bristol-Myers Squibb, Novartis, Pfizer, Adlai-Nortye (RF—institutional); **Carl Amireault**: Taiho, Celgene, Pfizer, Amgen (SAB), Taiho, Celgene, Amgen, Pfizer, Bristol-Myers Squibb, Janssen, AstraZeneca, Merck, Novartis (other—presentations); **Anne-Sophie Lemay**: Alexion (SAB); **Frédéric Lemay**: Pfizer, Bayer, Takeda, Taiho (C/A), Merck, Bristol-Myers Squibb, Novocure (RF), Esperas Pharma Inc., Ocellaris Pharma Inc. (other—board of directors); **Francine Aubin**: Taiho Pharma (H), Amgen, Shire, Celgene, Bristol-Myers Squibb, Pfizer (SAB), Merck, Bristol-Myers Squibb (RF—institutional). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

References

1. Longley DB, Harkin DP, Johnston PG. 5-fluorouracil: Mechanisms of action and clinical strategies. Nat Rev Cancer 2003;3:330–338.

2. Van Cutsem E, Twelves C, Cassidy J et al. Oral capecitabine compared with intravenous fluorouracil plus leucovorin in patients with metastatic colorectal cancer: Results of a large phase III study. J Clin Oncol 2001;19:4097–4106.

3. Henricks LM, Opdam FL, Beijnen JH et al. DPYD genotype-guided dose individualization to improve patient safety of fluoropyrimidine therapy: Call for a drug label update. Ann Oncol 2017;28:2915–2922.

4. Morel A, Boisdron-Celle M, Fey L et al. Clinical relevance of different dihydropyrimidine dehydrogenase gene single nucleotide polymorphisms on 5-fluorouracil tolerance. Mol Cancer Ther 2006;5:2895–2904.

5. van Kuilenburg AB, Muller EW, Haasjes J et al. Lethal outcome of a patient with a complete dihydropyrimidine dehydrogenase (DPD) deficiency after administration of 5-fluorouracil: Frequency of the common IVS14+1G>A mutation causing DPD deficiency. Clin Cancer Res 2001;7:1149–1153.

6. Meulendijks D, Henricks LM, Sonke GS et al. Clinical relevance of DPYD variants c.1679T>G, c.1236G>A/HapB3, and c.1601G>A as predictors of severe fluoropyrimidine-associated toxicity: A systematic review and meta-analysis of individual patient data. Lancet Oncol 2015;16:1639–1650.

7. Terrazzino S, Cargnin S, Del Re M et al. DPYD IVS14+1G>A and 2846A>T genotyping for the

prediction of severe fluoropyrimidine-related toxicity: A meta-analysis. Pharmacogenomics 2013; 14:1255–1272.

8. Lee AM, Shi Q, Pavey E et al. DPYD variants as predictors of 5-fluorouracil toxicity in adjuvant colon cancer treatment (NCCTG N0147). J Natl Cancer Inst 2014;106:dju298.

9. Boige V, Vincent M, Alexandre P et al. DPYD genotyping to predict adverse events following treatment with fluorouracil-based adjuvant chemotherapy in patients with stage III colon cancer: A secondary analysis of the PETACC-8 randomized clinical trial. JAMA Oncol 2016;2: 655–662.

10. Toffoli G, Giodini L, Buonadonna A et al. Clinical validity of a DPYD-based pharmacogenetic test to predict severe toxicity to fluoropyrimidines. Int J Cancer 2015;137:2971–2980.

11. Deenen MJ, Meulendijks D, Cats A et al. Upfront genotyping of DPYD*2a to individualize fluoropyrimidine therapy: A safety and cost analysis. J Clin Oncol 2016;34:227–234.

12. Schwab M, Zanger UM, Marx C et al. Role of genetic and nongenetic factors for fluorouracil treatment-related severe toxicity: A prospective clinical trial by the German 5-FU Toxicity Study Group. J Clin Oncol 2008;26:2131–2138.

13. Common Terminology Criteria for Adverse Events (CTCAE). Version 5. Bethesda, MD: National Cancer Institute, 2017. Available at https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf. Accessed December 15, 2018.

14. Henricks LM, Lunenburg C, de Man FM et al. DPYD genotype-guided dose individualisation of fluoropyrimidine therapy in patients with cancer: A prospective safety analysis. Lancet Oncol 2018;19: 1459–1467.

15. Cunningham D, Zalcberg JR, Rath U et al. Final results of a randomised trial comparing 'tomudex' (raltitrexed) with 5-fluorouracil plus leucovorin in advanced colorectal cancer. ''Tomudex'' Colorectal Cancer Study Group. Ann Oncol 1996;7:961–965.

16. Cocconi G, Cunningham D, Van Cutsem E et al. Open, randomized, multicenter trial of raltitrexed versus fluorouracil plus high-dose leucovorin in patients with advanced colorectal cancer. Tomudex Colorectal Cancer Study Group. J Clin Oncol 1998;16:2943–2952.

17. Varughese LA, Lau-Min KS, Cambareri C et al. DPYD and UGT1A1 pharmacogenetic testing in patients with gastrointestinal malignancies: An overview of the evidence and considerations for clinical implementation. Pharmacotherapy 2020;40:1108–1129.

18. Henricks LM, Lunenburg C, de Man FM et al. A cost analysis of upfront DPYD genotype-guided dose individualisation in fluoropyrimidine-based anticancer therapy. Eur J Cancer 2019;107:60–67.

19. Ploylearmsaeng SA, Fuhr U, Jetter A. How may anticancer chemotherapy with fluorouracil be individualised? Clin Pharmacokinet 2006;45: 567–592.

20. Meulendijks D, Henricks LM, Jacobs BAW et al. Pretreatment serum uracil concentration as a predictor of severe and fatal fluoropyrimidine-associated toxicity. Br J Cancer 2017;116: 1415–1424.

21. Benson AB 3rd, Schrag D, Somerfield MR et al. American Society of Clinical Oncology recommendations on adjuvant chemotherapy for stage II colon cancer. J Clin Oncol 2004;22:3408–3419.

22. Fluorouracil [prescribing information]. Irvine, CA: Spectrum Pharmaceuticals, 2016. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/012209s040lbl.pdf. Accessed July 10, 2020.

23. Van Cutsem E, Cervantes A, Adam R et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. Ann Oncol 2016;27:1386–1422.

24. European Medicines Agency. Fluorouracil and fluorouracil related substances (capecitabine, tegafur and flucytosine) containing medicinal products. European Medicines Agency Web site. Published April 30, 2020. Available at https://www.ema.europa.eu/en/medicines/human/referrals/fluorouracil-fluorouracil-related-substances-capecitabine-tegafur-flucytosine-containing-medicinal. Accessed July 10, 2020.

25. Béland M. Traitements à base de fluoropyrimidines: Meilleures strategies pour réduire le risque de toxicités sévères causées par une déficience en dihydropyrimidine déshydrogénase. Quebec City, Quebec, Canada: Institut National d'Excellence en Santé et en Services Sociaux, 2019. Available at https://www.inesss.qc.ca/fileadmin/doc/INESSS/Rapports/Oncologie/INESSS_DPYD_Traitements.pdf. Accessed July 10, 2020.

26. Loriot MA, Ciccolini J, Thomas F et al. Dihydropyrimidine dehydrogenase (DPD) deficiency screening and securing of fluoropyrimidine-based chemotherapies: Update and recommendations of the French GPCO-Unicancer and RNPGx networks [in French]. Bull Cancer 2018;105:397–407.

27. Kuhn JG. Fluorouracil and the new oral fluorinated pyrimidines. Ann Pharmacother 2001;35: 217–227.