Acta Clinica Belgica

International Journal of Clinical and Laboratory Medicine

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/yacb20

Joint Belgian recommendation on screening for DPD-deficiency in patients treated with 5-FU, capecitabine (and tegafur)

Veerle Casneuf , Ivan Borbath , Marc Van den Eynde , Yolanda Verheezen , Wim Demey , Alain G Verstraete , Kathleen Bm Claes , Vincent Haufroid & Karen P Geboes

To cite this article: Veerle Casneuf , Ivan Borbath , Marc Van den Eynde , Yolanda Verheezen , Wim Demey , Alain G Verstraete , Kathleen Bm Claes , Vincent Haufroid & Karen P Geboes (2021): Joint Belgian recommendation on screening for DPD-deficiency in patients treated with 5-FU, capecitabine (and tegafur), Acta Clinica Belgica, DOI: 10.1080/17843286.2020.1870855

To link to this article: https://doi.org/10.1080/17843286.2020.1870855

Published online: 11 Jan 2021.

ACTA CLINICA BELGICA
https://doi.org/10.1080/17843286.2020.1870855

Taylor & Francis
Taylor & Francis Group

ARTICLE

Joint Belgian recommendation on screening for DPD-deficiency in patients treated with 5-FU, capecitabine (and tegafur)

Veerle Casneuf[a], Ivan Borbath[b], Marc Van den Eynde[c], Yolanda Verheezen[d], Wim Demey[e], Alain G Verstraete[f], Kathleen Bm Claes[g], Vincent Haufroid[h]* and Karen P Geboes[i]*

[a]Department of Gastroenterology, OLV Aalst, Aalst, Belgium; [b]Department of Hepatology and Gastroenterology, University Hospital St Luc/UCLouvain, Woluwe; [c]Department of Oncology, University Hospital St Luc/UCLouvain, Woluwe; [d]Department of Oncology, Jessa Ziekenhuis, Hasselt; [e]Department of Oncology, AZ Klina, Brasschaat Belgium; [f]Department of Clinical Biology, UZ Gent, Gent; [g]Department of Medical Genetics, UZ Gent, Gent; [h]Department of Toxicology and Applied Pharmacology, University Hospital St Luc/UCLouvain, Woluwe; [i]Department of Gastroenterology, UZ Gent, Gent

ABSTRACT

Objectives: Fluoropyrimidines such as 5-Fluorouracil (5-FU), capecitabine and tegafur are drugs that are often used in the treatment of maliginancies. The enzyme dihydropyrimidine dehydrogenase (DPD) is the first and rate limiting enzyme of 5-FU catabolism. Genetic variations within the DPYD gene (encoding for DPD protein) can lead to reduced or absent DPD activity. Treatment of DPD deficient patients with fluoropyrimidines can result in severe and, rarely, fatal toxicity. Screening for DPD deficiency should be implemented in practice.

Methods: The available methods in routine to screen for DPD deficiency were analyzed and discussed in several group meetings involving members of the oncological, genetic and toxicological societies in Belgium: targeted genotyping based on the detection of 4 DPYD variants and phenotyping, through the measurement of uracil and dihydrouracil/uracil ratio in plasma samples.

Results: The main advantage of targeted genotyping is the existence of prospectively validated genotype-based dosing guidelines. The main limitations of this approach are the relatively low sensitivity to detect total and partial DPD deficiency and the fact that this approach has only been validated in Caucasians so far. Phenotyping has a better sensitivity to detect total and partial DPD deficiency when performed in the correct analytical conditions and is not dependent on the ethnic origin of the patient.

Conclusion: In Belgium, we recommend phenotype or targeted genotype testing for DPD deficiency before starting 5-FU, capecitabine or tegafur. We strongly suggest a stepwise approach using phenotype testing upfront because of the higher sensitivity and the lower cost to society.

Background on the use of 5-Fluorouracil and toxicity

Fluoropyrimidines such as 5-Fluorouracil (5-FU), capecitabine and tegafur, are pyrimidine analogues, antineoplastic agents which act as an antimetabolite to uracil. 5-FU is administered intravenously and capecitabine and tegafur are oral prodrugs.

5-FU inhibits activity of thymidilate synthase and thus deoxythymidine monophosphate synthesis through complex formation. This results in phase-specific DNA-synthesis inhibition. Deoxy-fluoronucleosides inhibit de novo synthesis of pyrimidine nucleotides.

By the above-mentioned mechanisms, 5-FU interferes with cell division and growth, acting mainly on tissues with rapid cell division, such as bone marrow, epithelium of the gastrointestinal tract and oral mucosa.

5-FU and capecitabine are indicated mainly for the treatment of gastrointestinal malignancies (gastric, colon, pancreatic, oesophageal, rectal cancer, cholangiocarcinoma), head and neck cancer and breast cancer. Tegafur, not frequently used in Belgium, is administered orally (with gimeracil and oteracil) for gastric cancer, combined with cisplatinum.

Indications for treatment vary over time. For instance: the use of FEC (5-FU, epirubicine, cyclofosfamide) in breast cancer has decreased over time, but FOLFIRINOX (5-FU, irinotecan and oxaliplatin) is prescribed extensively in pancreatic cancer, a tumor that is rising in incidence. There are regional differences in availability of certain drugs because of regulatory or financial reasons.

Only a small fraction of 5FU or capecitabine is transformed into active cytotoxic metabolites. More than 80% of the administered dose is detoxified and excreted as metabolites (mainly fluoro-beta-alanine, FBAL) in urine.

CONTACT Karen P Geboes vincent.haufroid@uclouvain.be Department of Gastroenterology, UZ Gent, Gent

*Both authors contributed equally

Initiated by the Belgian Group of Digestive Oncology (BGDO) and endorsed by the Belgian Society of Medical Oncology (BSMO), College of Genetics (CG), Toxicological Society of Belgium and Luxembourg (BLT)

The *DPYD* gene encodes for the synthesis of an enzyme called dihydropyrimidine dehydrogenase (DPD), involved in the breakdown of uracil and thymine when they are not needed. DPD is the first and rate limiting enzyme of 5-FU catabolism, and has a pivotal role in 5-FU and prodrugs elimination patterns. Deficiency of this enzyme leads to the drug buildup that causes fluoropyrimidine toxicity. Genetic variations within the *DPYD* gene (encoding for DPD protein) can lead to reduced or absent DPD activity and individuals who are heterozygous or homozygous/compound heterozygous for these variations may have partial or complete DPD deficiency. Treatment of DPD deficient patients with fluoropyrimidines can therefore result in severe and, rarely, fatal toxicity.

The first case of a fatal outcome caused by DPD deficiency has already been published in 1985. Drug labels include a safety warning for DPD deficiency and EMA and FDA as well as oncological societies recommend not to use 5-FU and its prodrugs in case of total DPD deficiency. In these cases, toxicity appears early on, in the first treatment cycle. An antidote, uridine triacetate (Vistogard®), exists but is very difficult to obtain in Europe and should be administered within 96 hours after administration of 5-FU.

Epidemiology of DPD deficiency

In the Caucasian population, approximately up to 8% has a partial DPD deficiency and up to 0.5% is fully DPD deficient [1–4]. Not all toxicities experienced during treatment with 5FU can be attributed to DPD deficiency. In the literature, it is reported that about 50% of overall 5-FU related toxicities could be attributed to diminished DPD activity [1–3].

In France, among 100 000 patients exposed to capecitabine or 5-FU yearly, nearly 8000 patients would have a partial DPD deficiency and up to 500 would be fully DPD deficient.

In Belgium, with 17 000 new patients potentially exposed to capecitabine or 5FU yearly, this would amount to 1300 patients with a partial DPD deficiency and up to 85 fully DPD deficient.

Several questions need to be addressed. What would be the best strategy to identify patients with total or partial DPD deficiency? What is the performance of available tests? How would we implement the tests in daily practice? How would we ensure an adequate turn-around-time (TAT), which should be kept within 7, max 14 days? And finally, what would be the cost?

Available screening tests [5]

Currently, two methods are available in routine to screen for DPD deficiency:

- The genotyping approach, based on the detection of four *DPYD* variants known to be associated with decreased DPD activity (*2A, *13, p.D949V and HapB3). This approach is also known as 'targeted *DPYD* genotyping' and is performed on DNA extracted from EDTA blood.
- The phenotyping approach, or the estimation of the DPD activity, through the measurement of uracil (U) and dihydrouracil/uracil ratio (UH2/U) in plasma.

Genotyping

A recent update Table 1 from the Clinical Pharmacogenetics Implementation Consortium (CPIC) now recommends to search for at least 4 *DPYD* variants associated with either a total loss (*DPYD*2A*, rs3918290, c.1905 + 1 G > A and *DPYD*13*, rs55886062, c.1679 T > G) or a reduced function (rs67376798, c.2846A>T, p.Asp949Val and HaplotypeB3, rs75017182, c.1129–5923 C > G/rs56038477, c.1236 G > A, p.E412E/rs56276561, c.483 + 18 G > A) of the DPD enzyme [4].

However, not all toxicity related to DPD deficiency can be explained by these four variants in the *DPYD* gene. For instance, in one study, complete *DPYD* sequencing in a subgroup with low enzyme activity and without *DPYD*2A* variant revealed 10 genetic variants, of which 4 had not been described previously [6]. Presence of other variants in regions of the *DPYD* gene that have not been sequenced and genetic variants in other (i.e., modifier) gene regions (e.g., miR27a and miR27b) that determine DPD enzyme activity might be the reason that we cannot explain all cases of a decreased enzyme activity even with full *DPYD* sequencing. In addition, other (e.g., environmental) factors determine part of DPD enzyme activity. Furthermore, it is not unlikely that comedication can influence the expression of the DPD enzyme. Also,

Table 1. Most frequent alleles found, based on a presentation of V haufroid, BGDO april 2019.

Haplotype	rsID	Nucleotide change	Protein change	Allele Functional Status	Activity Score	Ref
*2A	rs3918290[a]	c.1905 + 1 G > A	N/A	No function	0	14
*5	rs1801159	c.1627A>G	p.I543V	Normal	1	14
*9A	rs1801265	c.85 T > C	p.C29R	Normal	1	15
*13	rs55886062	c.1679 T > G	p.I560S	No function	0	14
	rs67376798	c.2846A>T	p.D949V	Decreased	0,5	16
HapB3	rs75017182, rs56038477, rs56276561	c.1129–5923 C > G, c.1236 G > A, c.483 + 18 G > A	N/A, p.E412E, N/A	Decreased	0,5	17

a high variability of DPD activity for a same variant has been demonstrated [6]. The sensitivity of targeted *DPYD* genotyping is 25%, the specificity is 95% [4,7,8].

Dosing recommendations published for capecitabine and 5-FU are based on a **scoring system** where alleles with a total loss of activity are attributed a score of 0, alleles with reduced activity a score of 0.5 and alleles with normal activity a score of 1. Then, the activity score for the genotype is calculated as the sum of the scores obtained from maternal and paternal alleles and a normal individual will have a score of 2.

In terms of dosing recommendations, for an activity score of 1.5, it was initially recommended to reduce the dose by 25% to 50%, for an activity score of 1, to reduce the dose by 50% and for activity scores of 0.5 and 0, to avoid – when possible – treatment using 5-FU or capecitabine [4]. These dosing guidelines recommended by the CPIC have been tested in a prospective pharmacogenomics (PGx) study at the end of 2018 [7]. Briefly, the authors showed that a 50% dose reduction in *DPYD*2A* and *DPYD*13* heterozygous patients was adequate in terms of drug safety while a larger dose reduction of 50% (instead of 25%) would probably also be necessary in c.2846A>T and c.1236 G > A (HapB3) carriers. They concluded that prospective *DPYD* targeted genotyping was feasible and cost-efficient in routine clinical practice and that implementation of *DPYD* genotype-guided individualized dosing should be a new standard of care [8] Figure 1.

In summary, the main advantages of the targeted genotyping approach are (i) its simplicity of implementation in terms of pre-analytical and analytical conditions and (ii) the existence of prospectively validated genotype-based dosing guidelines. However, the main limitations of this approach are (i) the quite low sensitivity to detect total (and partial) DPD deficiency and (ii) the fact that this approach has only been validated in Caucasians so far [1–4].

Phenotyping

To overcome the main limitations of the targeted genotyping test, a phenotyping approach based on the measurement of U and UH2 in plasma **before treatment** has been proposed. Plasma concentrations of U and UH2 are commonly measured by high

BGDO recommendation DPD-deficiency screening

Genotyping and Dose Adaptations:

- CPIC made a proposal for calculation of the gene activity based on the detection of the 4 principal variants, i.e. *DPYD*2A, DPYD*13, c.2846A>T* and *HapB3 (7)*:
    - *DPYD*2A* and *DPYD*13* alleles lead to a NON functional enzyme (Activity score 0): in case of homozygous patients, there is a contra-indication for administration of 5-FU and capecitabine.
    - It was originally suggested that *DPYD c.2846A>T* and *HapB3* have a reduced DPD activity of 50% (Activity score 0.5), but recent insights suggest an even lower activity and score (Activity score 0) .
    - Normal alleles (absence of any of the 4 variants) have a normal DPD activity (Activity score 1).

Activity should be counted for each allele and summed

If genotype score 2, normal dose

If genotype score 1,5 or 1, 50% of the dose

If genotype score 0,5 or 0, contraindication

At the second cycle, the doses should be reconsidered depending on the tolerance of the treatment and discussion with the pharmacist if possible.

Figure 1. Genotyping and dose adaptations.

performance liquid chromatography (HPLC) with different possible detection methods (UV spectrophotometry, mass spectrometry). Nowadays, most of the methods are based on highly sensitive and specific tandem mass spectrometry (LC-MS/MS) technology and results can be compared between laboratories because external quality control programs are available. High specificity, but more importantly, high sensitivity has been proven when performed in correct analytical conditions [1,2,9]. Three prospective observational studies assessed the performance of DPD phenotyping [9–11]. The original study was conducted in 252 colorectal cancers treated with intravenous 5-FU. The authors reported fairly similar results between UH2/U and plasma U regarding grade 3–4 toxicity (sensitivity = 82% and 88%; specificity = 78% and 69%, respectively). This study showed that the clearance of 5-FU was significantly correlated with U plasma concentration (inverse correlation) whereas it was not correlated with the UH2/U ratio [9]. The two other studies concluded that U was more effective than UH2/U in predicting the toxicity of capecitabine [10,11]

Both UH2/U ratio and U are continuous variables. Interpretation thus requires the determination and the validation of threshold values to distinguish patients with DPD deficiency from non-deficient patients. The literature available regarding UH2/U threshold is scarce and suggests large heterogeneity between laboratories. This is primarily due to the variability in the analytical methods used at that time (HPLC with UV detection, diode array or MS-MS) and to analytical interference in UH2 determination using non-LC-MS /MS methods. In contrast, the three independent prospective studies previously cited converge remarkably on the threshold value of U determining a risk of toxicity: greater than 15 ng/mL for the historical study and 16 ng/mL for the other two, leading to a general consensus for a cut-off at 14 ng/mL [9–12]. It is commonly admitted that U > 100 ng/mL is associated with DPD total deficiency (although this could not be validated prospectively, given the rarity of this phenotype) [2,9–12] Figure 2.

In summary, the main advantages of the phenotyping approach are (i) a better sensitivity, compared with the genotyping approach, to detect total and partial DPD deficiency and (ii) its interpretation which is not dependent of the ethnic origin of the patient. However, it must be stressed that the main limitation of the phenotyping test is the very strict pre-analytical requirements. Indeed, U level rapidly increases in whole blood mainly when the sample is kept at room temperature and the maximum delay for centrifugation and plasma freezing is 1h30 after blood collection. Furthermore, phenotype-based dosing recommendations still need to be validated in prospective trials.

Other tests

Full *DPYD* sequencing can be used in order to detect all variants. This test cannot be considered a routine test yet because several variants are still of unknown significance. However; in case of absence of correlation between phenotype and targeted genotype, it would be important to screen for other variants in order to improve our knowledge and improve clinical decisions in the future. Complementation of full *DPYD* sequencing with phenotyping may lead to more adequate interpretation of variants of unknown clinical significance. Its sensitivity should still be lower than phenotyping approach because some DPD deficiencies are also related to post-transcriptional changes in *DPYD* gene (mir-27,).

Somatic testing on *DPYD* variants on tumor tissue is not advocated. Although frequencies of genetic alterations may overlap between somatic and germline testing, a somatic tumor mutation is not predictive for a germline mutation. It has previously been shown that tumoral DNA is not suitable to determine the germline *CYP2D6* genotype for the prediction of tamoxifen responsiveness [13]. No dose adaptations can be suggested on the basis of a somatic finding only. A patient with a suggestion of a *DPYD* variant in tumor tissue will have to undergo subsequent germline analysis, delaying the start of treatment.

Implementation, technical aspects, cost and availability in Belgium

Genotyping is performed on whole blood (EDTA tube). Samples should be kept at room temperature.

(a) Targeted genotyping: 'Short cut' to four most important *DPYD* variants (DPYD*2A, DPYD*13, c.2846A>T and HapB3 of the *DPYD* gene). The cost of the test is € 160.50, € 8.68 for the patient. TAT around 10 days.
(b) Full DPYD sequencing: All variants. The cost of the test is € 369.57; € 8.68 for the patient. TAT 2 (–4) weeks.

In order to improve TAT, it is best to send samples directly to the performing labs, using the correct application form.

Labs that are currently performing targeted genotyping are:

- Centre de Génétique Humaine – CHU Sart-Tilman
- Centrum Menselijke Erfelijkheid – KULeuven
- Centre de Génétique Humaine – Cliniques universitaires St-Luc, UCLouvain
- Centrum Medische Genetica – UZ Gent

BGDO recommendation DPD-deficiency screening

Phenotyping and Dose Adaptations:

Different studies have set the cut-off for partial DPD deficiency as determined by uracil at 14ng/mL (1,2, 9-12).

There is less evidence suggesting a cut-off for total DPD deficiency (severe toxicity): a value of 100 ng/ml is currently used by experts and recommendations (2).

- A value of uracil ≥ 100 ng/mL is considered as compatible with total DPD deficiency (provided preanalytical aspects have been respected) and administration of 5-FU or capecitabine is contra-indicated. Risk of severe toxicity due to fluoropyrimidines is very high.
- A value of uracil between 14 ng/mL and < 100 ng/mL is considered as compatible with a partial DPD deficiency and associated with an increased risk of toxicity on fluoropyrimidines, so dose adaptations should be made. Often, a dose reduction of 50% is chosen (expert recommendation).
- A value of uracil < of = 14 ng/mL is considered as compatible with a normal DPD activity (12).

- Genotyping should be performed when the phenotyping test shows a value above 14 ng/mL (up to maximum 15% of the patients), because dose adaptations are better validated up to now for the 4 most important variants (see CPIC recommendation).

- Both UH2/U and uracil should be reported by the laboratory to the clinicians, because UH2/U ratio can give additional and potentially useful information (12).

Figure 2. Phenotyping and dose adaptations.

Labs that also perform *DPYD* sequencing of all variants are:

- Centre de Génétique Humaine-Cliniques universitaires St-Luc, UCLouvain
- Centrum Medische Genetica – UZ Gent

Phenotyping is performed using chromatography (HPLC-UV/HPLC diode array detection/HPLC-MS/MS) on blood samples with anticoagulant and without separating gel (10 ml heparin tube). TAT is around 10 days maximum when the analysis is performed on a weekly basis.

Pre-analytical conditions are crucial:

- Delay between blood sampling and centrifugation should be <1h30 when the sample is kept at room temperature and <4 h at 4°C
- The sample should be centrifuged at 4°C, with subsequent immediate freezing of the plasma
- Plasma samples should be kept at −20°C before analysis (also during transportation between different centres)

The results of the phenotyping test are **unreliable** if these precautions have not been taken and the test must be repeated with a new blood sample. All laboratories performing the test should participate to an external quality control program to certify the analytical phase.

The cost of the test is € 35–40 for the patient, currently not reimbursed.

Labs that are currently performing phenotyping tests are:

- Cliniques universitaires St-Luc, UCLouvain
- CHU Sart-Tilman
- UZ Gent
- Labo Klinische Biologie, Onze-Lieve-Vrouwziekenhuis – Aalst

It is recommended to test for DPD deficiency before starting 5FU-based chemotherapy. In order not to delay treatment, oncologists should implement phenotype and/or targeted genotype testing early in the management of malignancies requiring fluoropyrimidines. In order not to lose time through shipment, it is necessary to send blood samples directly to the labs performing the tests. Both phenotyping and targeted genotyping test can be performed simultaneously, or a stepwise procedure can be implemented, first performing phenotyping because of its higher sensitivity followed by genotyping for uracilemia above the threshold of 14 ng/mL. However, in order not to lose time with this stepwise procedure, the flow of samples has to be secured, e.g. by already taking two blood samples before initiation of 5-FU and sending the second sample to the genetic laboratory immediately when a high uracil (or a low UH2/U ratio) is detected.

- If we calculate 17 000 new tests per year in Belgium, the cost for screening all patients would amount up to 2.5 million euro for targeted genotyping. The cost of performing screening with phenotyping alone would be up to 680 000 euro.
- If we would use a stepwise approach, estimating that up to 15% of patients would have an elevated uracil and require genetic testing, the cost would be around 1 million euro.

International guidelines and proposals

The need for an upfront genotyping or phenotyping strategy has been discussed in other European countries and at the European level.

Targeted genotyping of the four most important *DPYD* variants before starting fluoropyrimidine has been implemented in the Netherlands after the publication of the prospective safety analysis on *DPYD* genotype-guided dose individualization of fluoropyrimidine therapy and the cost-efficiency analysis [7,8]. The Clinical Pharmacogenetics Implementation Consortium also endorses genotype-guided dose individualization and publishes and updates guidelines [4].

France asked EMA (by PRAC) to take action at the EU level (3/2019) regarding the detection of the DPD deficient patients and the methods that should preferably be used. This led to the EMA statement in April 2020, recommending phenotype and/or genotype testing for DPD deficiency prior to using 5-FU, capecitabine or tegafur, endorsed in the ESMO guidelines [3].

Treatment with fluorouracil, capecitabine or tegafur-containing medicines is **contraindicated in patients with known complete DPD deficiency**. A reduced starting dose should be considered in patients with identified partial DPD deficiency. No further advice on specificities of the tests or guidance on optimal dosing methods are given.

In Belgium, we recommend phenotype or targeted genotype testing for DPD deficiency before starting 5-FU, capecitabine or tegafur. We strongly suggest a stepwise approach using phenotype testing upfront because of the higher sensitivity and the lower cost for the society.

Conclusion:

It is recommended to perform phenotype and/or genotype testing for DPD deficiency prior to using 5-FU, capecitabine or tegafur. In order not to delay treatment, oncologists should implement phenotype and/or (targeted) genotype testing early at diagnosis for patients in metastatic setting or patients that require neo-adjuvant chemotherapy and early after surgery in patients that need adjuvant treatment. Treatment with fluorouracil, capecitabine or tegafur-containing medicines is contraindicated in patients with known total DPD deficiency. A reduced starting dose should be considered in patients with identified partial DPD deficiency.

Pre-analytical conditions are critical when U and UH2/U are measured. In patients with U above 14 ng/mL, we recommend dose adjustments and genetic testing.

Targeted genotyping can also be performed immediately. In order to ensure a short TAT, EDTA blood samples should be sent as soon as possible to one of the reference laboratories. Specific and validated genotype-based dose adaptations are available for heterozygous or homozygous/compound heterozygous patients for one of the four best characterized variants, i.e. *DPYD*2A, DPYD*13, c.2846A>T* and *HapB3*.

For patients without total DPD deficiency, starting treatment with dose reductions, subsequent adjustments need to be discussed according to clinical tolerance [14–17].

Disclosure statement

No potential conflict of interest was reported by the authors.

References

[1] Dépistage du déficit en dihydropyrimidine déshydrogénase (DPD) et sécurisation des chimiothérapies à base de fluoropyrimidines: mise au point et recommandations nationales du GPCO-

Unicancer et du RNPGx. Bull Cancer. 2018;105 (4):397–407.
[2] Recherche de déficit en dihydropyrimidine déshydrogenase en vue de prévenir certaines toxicités sévères survenant sous traitement comportant des fluoropyrimidines (5-fluorouracile), Recommandations et référentiels, INCa, HAS, décembre 2018.
[3] EMA/229267/2020 fluorouracil and fluorouracil related substances Article 31 referral – EMA recommendations on DPD testing prior to treatment with fluorouracil, capecitabine, tegafur and flucytosine
[4] Amstutz U, Henricks LM, Offer SM, et al. Clinical pharmacogenetics implementation consortium (CPIC) guideline for dihydropyrimidine dehydrogenase genotype and fluoropyrimidine dosing: 2017 update. Clin Pharmacol & Ther. 2018;103(2):210–221.
[5] Haufroid V, Picard N. Genotyping versus phenotyming: the case of fluoropyrimidines. 2019;18(2):9–10. The IATDMCT compass.
[6] Coenen MJ, Paulussen ADC, Breuer M, et al. Evolution of dihydropyrimidine dehydrogenase diagnostic testing in a single center during an 8-year period of time. Curr Ther Res Clin Exp. 2018;90:1–7.
[7] Henricks LM, Lunenberg CATC, 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(11):1459–1467. .
[8] Henricks LM, Lunenburg CATC. De Man, FM et al, A cost analysis of upfront DPYD genotype-guided dose individualisation in fluoropyrimidine-based anticancer therapy. Eur J Canc. 2019;107: 60–67.
[9] Boisdron-Celle M, Remaud G, Traore S, et al. 5-Fluorouracil-related severe toxicity: A comparison of different methods for the pretherapeutic detection of dihydropyrimidine dehydrogenase deficiency. Cancer Lett. 2007;249(2):271–282. .
[10] 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(11):1415–1424. .
[11] Etienne-Grimaldi MC, Boyer JC, Beroud C, et al. New advances in DPYD genotype and risk of severe toxicity under capecitabine. PloS One. 2017;12(5):e0175998. .
[12] Houssiau H, Duck L, Carlier S, et al. A case of life-threatening toxicity following capecitabine treatment: advocacy for dihydropyrimidine dehydrogenase deficiency screening. Belg J Med Oncol. 2020;14 (4):151–154.
[13] Goetz MP, Sun JX, Suman VJ, et al. Loss of heterozygosity at the cyp2d6 locus in breast cancer: Implications for germline pharmacogenetic studies. J Natl Cancer Inst. 2015;107(2):dju401.
[14] Offer SM, Wegner NJ, Fossum CC, et al. Phenotypic profiling of DPYD variations relevant to 5-fluorouracil sensitivity using real-time cellular analysis and in vitro measurement of enzyme activity. Cancer Res. 2013 Mar 15;73(6):1958–1968.
[15] He Y-F, Wei W, Zhang X, et al. Analysis of the DPYD gene implicated in 5-fluorouracil catabolism in Chinese cancer patients. J Clin Pharm Ther. 2008 Jun;33(3):307–314.
[16] Offer SM, Fossum CC, Wegner NJ, et al. Comparative functional analysis of DPYD variants of potential clinical relevance to dihydropyrimidine dehydrogenase activity. Cancer Res. 2014 May 1;74(9):2545–2554.
[17] Nie Q, Shrestha S, Tapper EE, et al. Quantitative contribution of rs75017182 to dihydropyrimidine dehydrogenase mRNA splicing and enzyme activity. Clin Pharmacol Ther. 2017 Oct;102(4):662–670.