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Laboratory-Clinic Interface

Improving safety of fluoropyrimidine chemotherapy by individualizing treatment based on dihydropyrimidine dehydrogenase activity – Ready for clinical practice?

Didier Meulendijks [a,b,c,*], Annemieke Cats [d], Jos H. Beijnen [e,f], Jan H.M. Schellens [a,b,f]

[a] Department of Clinical Pharmacology, Division of Medical Oncology, The Netherlands Cancer Institute, Amsterdam, The Netherlands
[b] Division of Molecular Pathology, The Netherlands Cancer Institute, Amsterdam, The Netherlands
[c] Dutch Medicines Evaluation Board (CBG-MEB), Utrecht, The Netherlands
[d] Department of Gastroenterology & Hepatology, The Netherlands Cancer Institute, Amsterdam, The Netherlands
[e] Department of Pharmacy & Pharmacology, The Netherlands Cancer Institute, Amsterdam, The Netherlands
[f] Faculty of Science, Division of Pharmacoepidemiology and Clinical Pharmacology, Department of Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands

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ABSTRACT

Fluoropyrimidines remain the cornerstone of treatment for different types of cancer, and are used by an estimated two million patients annually. The toxicity associated with fluoropyrimidine therapy is substantial, however, and affects around 30% of the patients, with 0.5–1% suffering fatal toxicity. Activity of the main 5-fluorouracil (5-FU) metabolic enzyme, dihydropyrimidine dehydrogenase (DPD), is the key determinant of 5-FU pharmacology, and accounts for around 80% of 5-FU catabolism. There is a consistent relationship between DPD activity and 5-FU exposure on the one hand, and risk of severe and potentially lethal fluoropyrimidine-associated toxicity on the other hand. Therefore, there is a sound rationale for individualizing treatment with fluoropyrimidines based on DPD status in order to improve patient safety.

The field of individualized treatment with fluoropyrimidines is now rapidly developing. The main strategies that are available, are based on genotyping of the gene encoding DPD (*DPYD*) and measuring of pretreatment DPD phenotype. Clinical validity of additional approaches, including genotyping of *MIR27A* has also recently been demonstrated.

Here, we critically review the evidence on clinical validity and utility of strategies available to clinicians to identify patients at risk of developing severe and potentially fatal toxicity as a result of DPD deficiency. We evaluate the advantages and limitations of these methods when used in clinical practice, and discuss for which strategies clinical implementation is currently justified based on the available evidence and, in addition, which additional data will be required before implementing other, as yet less developed strategies.

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Introduction

5-Fluorouracil (5-FU) and its oral prodrugs capecitabine and tegafur play a key role in the treatment of colorectal, gastric, and breast cancer, and an estimated two million patients are treated with fluoropyrimidines annually [1–3]. While the majority of patients can be treated safely, a substantial proportion experiences severe, sometimes lethal, fluoropyrimidine-associated toxicity. In phase III studies of fluoropyrimidine monotherapy around 30% of the colorectal cancer patients treated with 5-FU or capecitabine experienced severe (CTC-AE grade $\geqslant 3$) treatment-related toxicity. Moreover, typically 10–20% of the patients is hospitalized for toxicity during treatment, and 0.5–1% suffers fatal toxicity [4–7]. Thus, fluoropyrimidine-associated toxicity is a well-recognized clinical problem which has a substantial impact on patients' quality of life.

In 1985, Tuchman et al. reported on a patient with familial pyrimidinemia (elevated serum uracil and thymine concentrations) who experienced severe, almost lethal, toxicity upon treatment with 5-FU [8]. This report provided the first evidence that a genetic defect in pyrimidine catabolism could be associated with fluoropyrimidine-associated toxicity. Diasio and colleagues

* Corresponding author at: Division of Clinical Pharmacology, Department of Medical Oncology, The Netherlands Cancer Institute, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands. Fax: +31 20 512 2050.
E-mail address: didier.meulendijks@gmail.com (D. Meulendijks).

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subsequently showed that metabolism of 5-FU after a 25 mg/m^2 test dose, was nearly absent in a second patient with familial pyrimidinemia, and that activity of the enzyme dihydropyrimidine dehydrogenase (DPD) was exceptionally low [9].

Now, thirty-one years later, it is well established that DPD enzyme activity is strongly associated with the pharmacology of 5-FU, and that DPD deficiency greatly increases patients' risk of severe and sometimes fatal 5-FU-induced toxicity [10–12].

Because reduced DPD activity results in a predictable change in 5-FU exposure, there is a sound rationale for individualizing treatment with fluoropyrimidines based on DPD activity [13–15]. The clinical validity – the ability to reliably predict severe toxicity – as well as clinical utility of *DPYD* genotype-guided dosing – the clinical value of the intervention to improve patient safety – has recently been demonstrated in a prospective study of *DPYD**2A genotype-guided dosing [16]. Other strategies, including those based on DPD phenotype, are being developed and are at varying stages of development in terms of demonstrating clinical validity and utility (Table 1). In this review, we evaluate the different available strategies for individualizing treatment with fluoropyrimidi-

Table 1
Strategies to identify patients at risk of severe fluoropyrimidine-associated toxicity.

Strategy	Principle	Main advantages	Main limitations	Available evidence on clinical validity[b]	Available evidence on clinical utility[c]	Expected feasibility in routine clinical practice[d]
Genotype-based approaches						
DPYD variants	Genotyping of germline DNA for deleterious mutations in *DPYD*	High diagnostic accuracy (results are unambiguous and the test is not influenced by environmental factors) Easy to implement in diagnostic laboratories	Limited sensitivity to identify DPD deficient patients Clinical validity established for a limited number of *DPYD* variants	+	+	+
MIR27A variants	Genotyping of mutations in *MIR27A* that influence DPD expression	High diagnostic accuracy Easy to implement in diagnostic laboratories	Limited data available on the functional effects of *MIR27A* on DPD *in vivo*	+–	–	+
Phenotype-based approaches						
DPD activity in PBMCs	Determination of DPD enzyme activity in PBMCs using an *ex vivo* assay[a]	Most direct way of measuring DPD activity High clinical sensitivity to identify DPD deficient patients	Difficult to implement in diagnostic laboratories Labor intensive/expensive	+	–	–
Endogenous uracil concentrations	Determination of plasma/serum uracil concentration as a surrogate for systemic DPD activity	Expected to have high clinical sensitivity to identify DPD deficient patients Patient friendly, only one sample necessary and no test doses necessary	Cut-off not yet established Moderately difficult to implement in diagnostic laboratories (requires LC–MS/MS) Factors influencing measurement unknown (e.g. food, medication, circadian rhythm of DPD)	+	–	+
2-^{13}C uracil breath test	Administration to the patient of an oral solution of 2-^{13}C-uracil and subsequent measurement of $^{13}CO_2$ concentrations in exhaled breath	No blood drawings necessary	Assesses larger metabolic pathway than only DPD activity, results are influenced by other enzymes Requires expensive materials (2-^{13}C-uracil) and specific equipment at hospital (including infrared spectrometer), or shipping to central laboratory (delaying test results)	+–	–	+–
Uracil test dose	Administration to the patient of an oral dose of uracil and subsequent determination of systemic exposure using pharmacokinetic measurements	Expected to have high clinical sensitivity to identify DPD deficient patients Relatively easy to implement in diagnostic laboratories (requires HPLC)	Logistically challenging Less patient friendly	–	–	+–

DPD = dihydropyrimidine dehydrogenase; LC–MS/MS = Liquid chromatography-tandem mass spectrometry; PBMCs = peripheral blood mononuclear cells.
[a] Apart from methods with radioactive substrates, also methods using degradation of 5-fluorouracil in PBMCs have been developed, but limited data on the validity of these methods is available [87].
[b] "+" = Clinical validity well-established; "+–" = Limited evidence on clinical validity; "–" = No evidence on clinical validity.
[c] "+" = Clinical utility demonstrated prospectively; "–" = No evidence on clinical utility.
[d] "+" = Well feasible in clinical practice; "+–" = Difficult to use in clinical practice but possible; "–" = Great difficulties regarding use in clinical practice.

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