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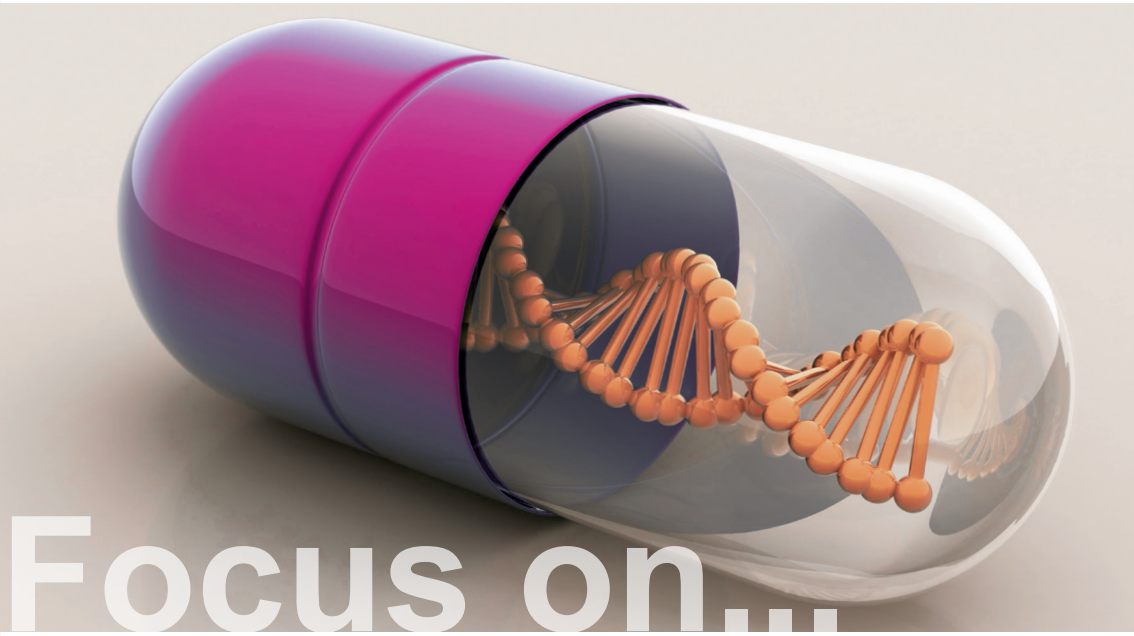

Focus on...

Fluoropyrimidines (5-FU / Xeloda®)

Prevention of toxicity and treatment optimisation

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5-FU in oncology

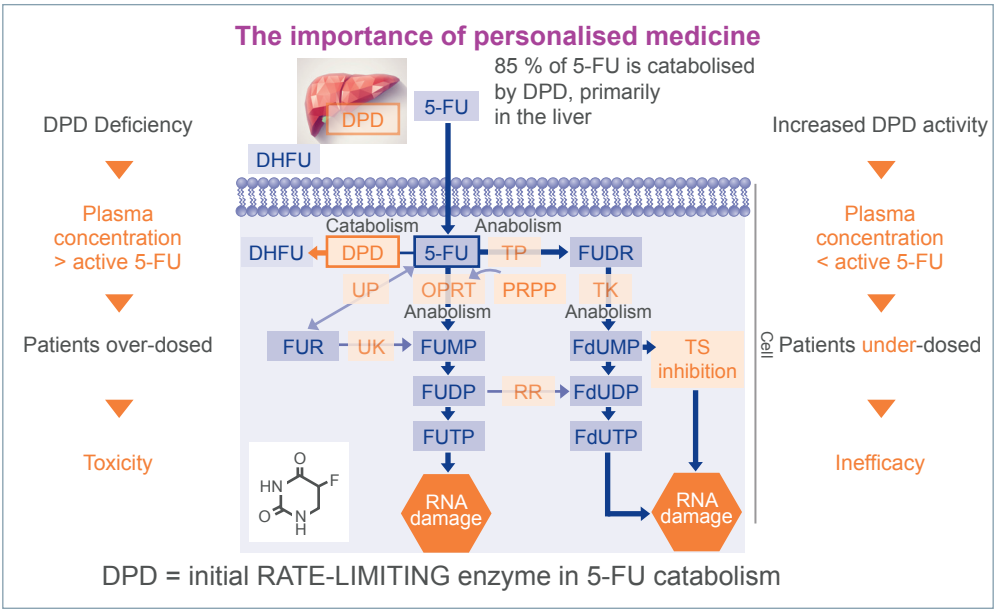
5-fluorouracil (5-FU) and its oral prodrugs, notably capecitabine (Xeloda®), are used in almost 60% of all chemotherapy protocols (colorectal, breast, pancreatic, ENT cancer).

Although generally well tolerated, these substances can cause severe toxicity, mainly in the digestive system, blood cells, the skin and mucosa.

The early severe toxicities of fluoropyrimidines are due in large part to the interindividual variability of their metabolism, mainly determined by the activity of dihydropyrimidine dehydrogenase (DPD).

Partial DPD deficiency can result in Grade III-IV toxicity in 20 to 25% of patients treated, which can be fatal in 0.2% of the total patient population.

Metabolism of 5-FU



- DPD is the enzyme responsible for 85% of the catabolism of 5-FU.
- Its activity is characterised by significant interindividual variability.
- DPD is subject to variability factors (physiopathological and genetic), causing major or complete enzyme deficits, which can in turn give rise to serious clinical complications.

Practical details

It is possible in routine clinical practice to combine pre-treatment screening for DPD deficiency with pharmacokinetically (PK)-guided dose management for DPD deficient patients.

- **Pre-treatment screening for DPD deficiency:** before the first course of chemotherapy treatment, identifies a contraindication to fluoropyrimidines (complete deficiency) or indicates a reduction in the initial dose (partial deficiency): 5-FU$^{ODPMTox™}$ test.
- **PK-guided dose management:** enables dosage to be adjusted as necessary in each course of treatment. An algorithm combining the patient's pharmacogenetic, pharmacological and physiopathological data allows personalised adjustment of the treatment between each course: 5FU$^{ODPM\ Protocol™}$ test.

The multiparametric approach of Eurofins Biomnis

The multiparametric approach includes:

- **Genotyping** (exploration of the 4 most frequent deleterious mutations of the gene responsible for coding DPD):
  - **D949V - rs67376798 - exon 22: 1.8%;**
  - **IVS14+1G>A - DPYD*2 - rs3918290, intron 14: 1.2%;**
  - **I560S - DPYD*13 - rs55886062 - exon 13: 0.3%;**
  - **Del TCAT - DPYD*7 - exon 4: 0.3%.**
- **Phenotyping** (assays of U and UH_2)
  - Pre-treatment plasma assays of endogenous uracil (U) and its metabolite, dihydrouracil (UH_2); determination of the DPD metabolisation index (UH_2/U).
- **Physiopathological characteristics** of patients (age, weight, height, tumour origin, etc.)
- **This data, in combination** with a CE-marked *in vitro* diagnostic medical device (proven algorithm 5-FU$^{ODPM\ Tox™}$), enables:
  - **The prediction of severe, grade III or IV, toxicities: 96%**
  - **The prediction of lethal toxicities: 100%**

It is important to note that:

- Genotyping, when used alone, is highly specific but not very sensitive (33%). This means that 67% of screened patients are at risk of severe toxicity.
- Phenotyping used alone is more sensitive (84%), but still leaves 16% of patients at risk of severe toxicity.
- The best results are obtained with the Eurofins Biomnis multiparametric approach. By using both genotyping and phenotyping, we can predict 100% of lethal toxicities and 96% of severe toxicities.

Evaluation of toxicity to fluoropyrimidines: 5-FU$^{ODPM\ Tox™}$

Before the initiation of treatment, to avoid severe toxic events

- **Experience with more than 20,000 patients: specificity 96%, sensitivity 96%**
- It is thus possible to almost completely prevent severe or fatal toxic events.

Practical details

- Sample: 1 tube of whole blood with lithium heparin (without gel separator): Refrigerated 2 tubes of lithium heparin plasma: Frozen
- **Turnaround time for results: 12 working days.**
- In the event of a risk of toxicity, a suggested first dose or contraindication to fluoropyrimidines is given in the results report, to support the clinician's prescription.

5-FU dosage adjustment: 5-FU$^{ODPM\ Protocol™}$

For duration of treatment, increasing efficacy while reducing toxicity

- PK-guided plasma assay of 5-FU taking into account the results for 5-FU$^{ODPM\ Tox™}$
- Enables dose adjustment to maintain 5-FU plasma concentration in the therapeutic range
- **Performance assessed in more than 90,000 courses of treatment to date.**

Practical details

- Sample to be taken between the 16th and 43rd hour of a 46-hour infusion
- In case of under- or over-dosing, the therapeutic advice on the results report enables adjustment of the dose for the next course of treatment.

Advantages of the Eurofins Biomnis multiparametric approach

The 5-FU$^{ODPM\ Tox™}$ and 5-FU$^{ODPM\ Protocol™}$ algortithms are CE marked medical devices which integrate the pharmacogenetic, pharmacological and physiopathalogical patient data for the following advantages:

- **5-FU$^{ODPMTox™}$ detects 96% of patients with partial deficiency and 100% of patients with total deficiencies**

- Preventing fatal toxicities in patients who are “potentially curable” (adjuvant treatments)
- Significant savings to the healthcare system: systematic screening is less expensive than treating toxicity
- PK-guided dose adjustment and treatment monitoring
- Personalising treatment to ensure optimum response
- Improving patient’s quality of life throughout treatment.

References

Boisdron-Celle M, Gamelin E, Morel A. Suivi thérapeutique du 5-fluorouracile (5-FU) [Therapeutic monitoring of 5-FU]. EMC Biologie médicale 2017 ;12 (2):1-7 [Article 90-45-0075-A].

Boisdron-Celle M, Morel A, Gamelin E. Dihydropyrimidine dehydrogenase deficiency and toxicity to fluoropyrimidine. Ann Biol Clin (Paris). 2010 Jan-Feb;68(1):27-32.

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Boisdron-Celle M, Capitain O, Farou R at al. Asco Annual Meeting 2013 Abstract 3601. Prevention of 5-FU-induced health-threatening toxicity by pre-therapeutic DPD deficiency screening: Medical and economic assessment of a multiparametric approach.

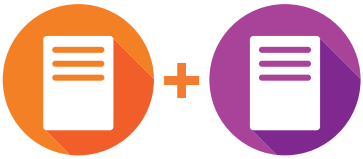
Requesting these tests

Referring Physician

5-FU ODPM Tox™

Before treatment

Order form* + Informed Consent form*



Stage 1 Genotyping of *DPYD*

Lithium heparin

Stage 2 UH_2/U Assays

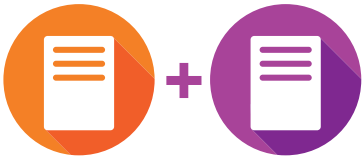
Lithium heparin frozen < 1h

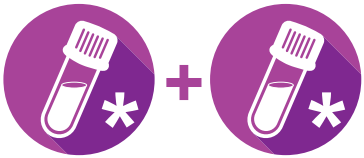
Lithium heparin frozen < 1h

5-FU ODPM Protocol™

During treatment

Order form* + Informed Consent form*





Lithium heparin frozen < 1h

Lithium heparin frozen < 1h

NB : for an infusion duration of 46 hours, sample between the 16th and 43rd hour

Eurofins Biomnis Laboratory

**Additional information and the related documents are available from*
www.eurofins.ie/biomnis

Summary

Pre-treatment screening 5-FU$^{ODPM\ Tox™}$
Avoid severe and lethal toxicities
1 time BEFORE the 1st course of treatment

COMPLETE DPD deficiency	PARTIAL DPD deficiency	NORMAL DPD activity
Avoid all treatment with fluoropyrimidines	Suggested reduced dose of 5-FU, **no reduction of efficacy**	**Standard dosage** for 1st course of treatment

PHARMACOKINETIC MONITORING 5-FU$^{ODPM\ Protocol™}$
1 sample per course of treatment

Dose adjustment according to plasma 5-FU

- Optimised dosing with no loss of efficacy
- Improved patient quality of life during treatment
- Reduction of grade III-IV toxicities
- NO lethal toxicities

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Eurofins Biomnis
Three Rock Road, Sandyford Industrial Estate,
Dublin 18, D18 A4C0, Ireland
Phone: 01 295 8545
E-mail: sales@eurofins-biomnis.ie
Web: www.eurofins.ie/biomnis