

SEVERE TOXICITY OF FLUOROPYRIMIDINES LINKED TO DIHYDROPYRIMIDINE DEHYDROGENASE (DPD) DEFICIENCY: EXPERIENCE OF NATIONAL INSTITUTE OF ONCOLOGY OF RABAT, MOROCCOEL. Mouhtadi S.,*¹ Filali N.,¹ Abahssain H.,² Harrak S.,¹ Mrabti H.,³ Boutayeb S.³ and Errihani H.⁴¹Resident in Medical Oncology, National Oncology Institute of Rabat Morocco.²Doctor Specialist Medical Oncology Department, National Oncology Institute of Rabat Morocco.³Professor of Medical Oncology Department, National Oncology Institute of Rabat Morocco.⁴Head of Medical Oncology Department, National Oncology Institute of Rabat Morocco.***Corresponding Author: EL. Mouhtadi S.**

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ABSTRACT

We report the experience of the National Institute of Oncology of Rabat of severe toxicities due to Fluoropyrimidines, linked to a deficiency in dihydropyrimidine dehydrogenase (DPD) in cancer patients.

INTRODUCTION

Fluoropyrimidines are cytotoxics widely used in medical oncology, belonging to the class of antimetabolites, a subclass of the pyrimidine analogues represented by 5-fluorouracil (5-FU), a fluorinated derivative of uracil, whose main mechanism of action is to inhibit DNA synthesis and capecitabine the oral fluorouracil prodrug.

They can induce severe toxicities, the incidence is estimated at around 20%, some of these toxicities are linked to a partial or complete dihydropyrimidine dehydrogenase deficiency, the enzyme responsible for the elimination of more than 80% of Fluoropyrimidines.

In this study, we report the experience of the National Oncology Institute of Rabat in the identification and management of severe toxicities of Fluoropyrimidines.

METHODOLOGY

This is a retrospective study spread over a period of 2 years (2018-2019), including all patients treated with Fluoropyrimidines and who have developed severe secondary toxicities according to the CTCAE v4.0 classification, and looking for a DPD deficiency in them, as well as their follow-up.

The search for DPD deficiency is done by genotyping, the DPYD gene which codes for the DPD enzyme, located on chromosome 1 with 23 exons, or by phenotyping techniques which aim to measure more directly the functional activity of the enzyme, and so has the potential capacity to identify all types of DPD deficiency, in particular complete deficits, in our context the search for DPD deficiency was carried out

exclusively by phenotyping.

RESULTS

In our pharmacovigilance survey, evaluating in real prescription situations the incidence of serious adverse effects (SAEs) in 610 patients, identified from the cancer registry of the National Institute of Oncology of RABAT and having received a fluoropyrimidine during their chemotherapy treatment, collected over a period of 2 years (from January 2018 to December 2019), 7% of the patients developed severe grade 3-4 toxicities, with only one death, of which only 5% were linked to a DPD deficiency.

The search for DPD deficiency was not systematic in our context; it was carried out in patients with severe toxicities, only one patient had a total deficiency the rest of the patients the deficiency was partial.

Toxicities are of rapid onset and progressive aggravation, essentially digestive, haematopoietic, skin and mucous membranes toxicities, more observed with bolus administration than with continuous infusion and in association with other treatments.

The management of toxicities by symptomatic treatment was carried out in the hospital environment. Some cases required intensive care.

Subsequent cancer management was marked either by a definitive cessation of Fluoropyrimidine treatment or by dose reductions in addition to appropriate supportive care.

DISCUSSION

Fluoropyrimidines are indicated for the treatment of colorectal, oesophageal, stomach, breast and upper aerodigestive tract cancers. They are present in approximately 45% of chemotherapy protocols, 99% of colorectal cancers patients and 88% of breast cancer patients being treated with fluoropyrimidines.^[1]

DPD, encoded by the DPYD gene, is an enzyme involved in the catabolism of endogenous (uracil and thymidine) and fluorinated (drug) pyrimidines. It is present in many tissues but its activity is maximal in circulating lymphocytes and hepatocytes. Thus, only a small fraction of 5-FU is anabolised into cytotoxic derivatives in tissues because the molecule is over-catabolised (80 - 85%) by DPD.^[2,3]

Patients with a significant DPD deficiency present an increased risk of severe toxicity with 5-FU or Capecitabine. DPD deficiencies can be:

- Partial, with a prevalence in Caucasians estimated between 3 and 8% according to the publications.^[4,5]
- Complete, with a prevalence estimated to be between 0.01 and 0.5%.^[4,5,6]

Toxicities associated with DPD deficiency are early, usually occurring during the first two cycles of chemotherapy.

In fact, the alteration in 5-FU metabolism caused by DPD deficiency leads, from the first cycle of chemotherapy, to an increase in 5-FU concentrations beyond the maximum tolerated concentration. As in our context the toxicities observed are rapidly onset and progressively worsen.

Severe toxicities under fluoropyrimidines, grade ≥ 3 , occur mainly in rapidly renewing tissues such as bone marrow (haematological toxicities: neutropenia, thrombocytopenia, anaemia), mucous membranes of the digestive tract (nausea and vomiting, mucositis, ulcerations of the oropharyngeal mucosa, diarrhoea) and skin cells (alopecia, dermatitis, palmoplantar erythrodermas).^[7]

The level of severity of these adverse effects is commonly graded according to the CTCAE (Common Terminology Criteria for Adverse Events) terminology, with severe toxicity grades 3, 4 and 5:

- Grade 3: a severe or medically significant adverse event, but not immediately life-threatening, leading to hospitalisation or prolongation of hospitalisation, interfering with the basic activities of daily living;
- Grade 4: life-threatening adverse event requiring emergency treatment;
- Grade 5: death related to the adverse event.
- Incidence data for severe toxicities are variable depending on :
- The heterogeneity of tumour types ;

- Fluoropyrimidine (5-FU or capecitabine) and the modes of administration considered (continuous infusion or bolus for 5-FU);
- The grade, the nature (global, haematological, digestive, cutaneous and/or neurological toxicities...) and the time of onset (first cycle, first two cycles, or even more) of the toxicities;
- The clinical characteristics of the patients included in the different studies (age, sex, renal function, performance status...)^[12]
- Other treatments possibly administered in association with fluoropyrimidines; and thus a potentialisation of toxic effects, which may lead to an overestimation of the incidence of serious adverse effects (SAEs). For example, Gilbert's syndrome, which affects 10% of the population and results from the presence of deleterious variants within the UGT1A1 gene, could be linked to an increased risk of diarrhoea and particularly severe neutropenia in patients treated with Irinotecan.

In our study, the incidence of these severe toxicities was observed more in bolus administration than in continuous infusion and in association with other treatments.

Early identification of patients with DPD deficiency becomes crucial.

In case of total deficiency, alternative treatments containing non-fluoropyrimidine compounds can be proposed,^[8]

For patients with a partial DPD deficiency, an initial dose reduction and an individual dose adjustment should be considered,^[9] depending on the pharmacokinetic follow-up.

Several techniques for exploring DPD activity are mentioned in the literature. The genotypic approach, which enables the detection of the different mutations in the gene coding for DPD located on chromosome 1p22.

However, the gene is complex and has many variable sequences and among the hundreds of polymorphisms (variants), only a minority is associated with enzymatic deficiency may explain the occurrence of the fluoropyrimidines severe toxicities.

Four DPYD variants (PYD*2A, DPYD*13, c.2846A>T and HapB3) whose functional impact is demonstrated in vitro, are considered to be associated with a significant risk of over-toxicity to fluoropyrimidines.

This low sensitivity corroborates the fact that not carrying a mutation does not guarantee good tolerance to fluoropyrimidines.^[7]

The phenotypic approach by measuring uracilemia (U) and calculating the dihydrouracil/uracil ratio (UH2/U) seems more reliable, due to the existence of a common

threshold of 16 ng/ml allowing the identification of partial DPD deficient individuals. A uracilemia value above 150 ng/ml was suggestive of a complete DPD deficiency.^[7]

An approach combining genotyping and phenotyping, according to the studies, clearly improves the sensitivity of screening for patients at risk of developing severe fluoropyrimidine toxicity.^[10]

The management of toxicities is carried out by symptomatic treatment, in our context it has been done in hospital with recourse in certain cases to intensive care.

It should be noted that there is an antidote to 5-FU intoxications, Vistogard® (uridine triacetate), but its interest remains very limited. Indeed, it must be prescribed within 96 hours after the end of fluoropyrimidine administration, its efficacy and safety not being established beyond this time. It is therefore not suitable for all serious toxicities.^[11]

Systematic screening for DPD deficiency with dosage adjustments of 5-FU and Capecitabine should significantly reduce the severe and lethal toxicities induced by these treatments, to improve patients lives, and to limit delays in cures, for the efficacy of Fluoropyrimidine-based chemotherapies.

Nevertheless, whatever the method used to research the DPD deficiency, will be able to avoid all the severe and lethal toxicities. On the one hand, DPD deficiencies explain only part of the toxicities linked to fluoropyrimidines and, on the other hand, all the toxicities arising from a combination of cytotoxic treatments incorporating a fluoropyrimidine cannot be attributed specifically to this molecule.

Furthermore, at present, no method is likely to be able to identify all patients with partial or complete DPD deficiency reliably in terms of sensitivity and positive predictive value.^[7]

CONCLUSION

Fluoropyrimidines are major drugs in the treatment of certain types of cancer, particularly digestive, breast and ENT cancers.

However, they can cause serious or even fatal toxicities, some of which are linked to a DPD deficiency responsible for the elimination of around 80% of the administered dose of 5-FU.

This deficiency may be partial or complete. Hence the need for its systematic dosage before starting treatment.

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