PREDICTING FLUOROPYRIMIDINE-RELATED TOXICITY : TURNING WISH TO WILL, THE PAMM-EORTC POSITION

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Fluoropyrimidines alone or in combination with other drugs rank among the most widely prescribed anticancer agents worldwide. Standard doses of 5-fluorouracil (5-FU) are overall claimed being associated with 20-40% severe adverse drug reactions (ADRs) and up to 1% of lethal toxicities isconsistently reported. Numerous clinical investigations have shown that complete dihydropyrimidine dehydrogenase (DPD) deficiency, a pharmacogenetic syndrome leading to total inability of detoxifying fluoropyrimidines in the liver, may be lethal. Other studies have suggested that severe ADRs may also be the consequence of relative overdosing from individual with partial DPD dysfunction and incomplete metabolic capacity of detoxifying 5-FU(1). Indeed, not all ADRs during 5-FU therapy are directly linked to impaired metabolism but identifying more systematically DPD deficiency may theoretically downsize the group of at risk patients. The quality of the assay, the reliability of gene variants, the robustness of recommendations for dose adjustments, and the cost-effectiveness of the approach has generated a debate within the oncology community.

A wide range of methods have been made available to establish the DPD status in patients scheduled for treatment with fluoropyrimidines. Today, most of them focus either on the screening for 4 allelic variants of the DPYD gene (i.e.,DPYD*2A, c.2846A>T, c.1679T>G and Haplotype B3) associated with reduction or complete loss of enzymatic function (2), or on phenotyping approaches mostly based upon the detection of increased uracil (U)plasma levels or monitoring of dihydrouracil(UH2)/U ratio in plasma (3).

A rising number of clinical studies have shown that upfront DPD-testing with adaptive dosing strategies could help reducing the incidence of early severe ADRs while maintaining efficacy when implemented in routine clinical practice (4, 5). In addition, cost-effectiveness of preemptive DPD screening has been repeatedly demonstrated (1,5). Consequently, various calls for update in drug labeling and/or implementation of DPD testing in routine clinical practice have been issued over the last decade by pharmacological societies in Europe.

However, anticipating DPD-related ADRs based on the sole evaluation of DPD activity remains challenging, mainly because toxicity may also be related to patient conditions such as age or performance status, but also because fluoropyrimidines are often used in various combinations with other drugs that are blurring the anticipation of fluoropyrimidine-ADRs in routine practice (6).As a consequence, oncologists remain hesitant in adopting pharmacologically-guided dosing. Indeed, DPYD genotyping may appear convenient and CE-IVD (Conformité Européenne-In vitro diagnostics) diagnostics are available in many academic centers. However, spreading their use for all patents in community hospitals and clinics may be challenging becausesome centers may not have implemented routine *DPYD* screening due to restrictions in the access to laboratory facility (or current facility may be overflooded by the number of demands) and the over-cost associated with the analysis is not fully covered by health insurances in some European countries. Furthermore, the high specificity of the assay is hampered by its low sensitivity, as less than 10% of the Caucasian population bears one of the 4 allelic variants routinely screened – a figure much lower than the incidence of severe toxicities usually reported with fluoropyrimidines. Basically, if there is a high probability that patients carrying a *DPYD* variant will develop toxicity, it remains uncertain whether or not patients who do not carry such variant can be treated safely at standard dose of fluoropyrimidines. On the other hand, DPD phenotyping suffers from the lack of comprehensive and prospective studies addressingits sensitivity and specificity; in addition to this, the quality of the analytical result is dramatically affected by the need of stringent conditions in sample handling, possible biases related to circadian variations or food intake, as well as longer turnaround times as compared with genotyping and substantially higher costs– making for years phenotyping tricky to implement as a part of a widespread screening strategy, apart from highly specialized centers.

All these issues as well as the negative position of ESMO (7) probably explain the reluctance of clinicians as well as of Health Authorities to take a strong position in favor of recommending systematic preemptive DPD screening. However, to prevent a lack of knowledge and media pressure from having a negative impact on patient confidence in safe and effective medicinal products, the European Medicines Agency and national health authorities such as the French ANSM are currently working on defining the best strategy to be undertaken at bedside to better predict, thus prevent, ADRs by fluoropyrimidines.

In the light of the consensus regarding the 4 *DPYD* allelic variants to be screened as part of best practice recommendations, plus recent efforts to identify relevant thresholds and optimal analytical conditions when phenotyping DPD (i.e., by focusing on U plasma levels rather than UH2/U ratio), the PAMM EORTC group strongly supports the prospective evaluation of DPD activity in patients scheduled for fluoropyrimidines. Despite its above-mentioned limitations, genotyping *DPYD* should

help detecting patients with homozygous mutations at risk of toxic-death, and providing appropriate dose-adjustments in the case of heterozygosis. When available, phenotyping patients should help to provide practitioners with a better insight on DPD function. Furthermore, further understanding *DPYD* variants of unknown significance and in this respect phenotyping could be a powerful approach to secure 5-FU administration. Overall, there are today a wide range of techniques and strategies that proved their clinical relevance to customize administration of 5-FU or capecitabine and time has come to turn wish to will.

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