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Letter to the Editor

Fluoropyrimidines and DPD testing: is there truly an inexorable link?

Gérard Milano

Oncopharmacology Unit, Centre Antoine Lacassagne, 33, Avenue de Valombrose – 061 89 Nice Cedex, France

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It is indisputable that fluoropyrimidines (FU) are still a mainstay of cancer chemotherapy in an era of innovating treatments including targeted therapy and immunotherapy. However, FU cause severe toxicities in 10–40% of patients and toxic deaths in 0.2–0.8% of patients, resulting in a real public health problem [1]. Dihydropyrimidine dehydrogenase (DPD), the key enzyme for FU catabolism, was identified more than 20 years ago by others and us as being responsible for placing patients at risk of toxicity when they present a reduced activity of this catabolic enzyme [2,3]. Approximately, 3–15% of patients are at risk for a partial DPD deficiency, while 0.1–0.5% display complete DPD deficiency [1]. Different approaches have been proposed to identify patients carrying a DPD deficiency. The first strategy is DPD phenotyping. This can be performed through direct measurement of DPD activity in blood mononuclear cells [4], or by indirect evaluation of DPD global activity through analysis of uracil and dihydrouracil in body fluids, mainly plasma [5]. Alternatively, it is possible to perform DPD genotyping in the light of a cumulated knowledge regarding *DPYD* gene variants [6]. Four well-established toxicity-associated *DPYD* variants (*DPYD**2A, c. 2846 A > T, c. 1679 T > G and c. 1236 G > A) have been described [7] and prospectively validated at a clinical level [8]. On this basis, guidelines for DPD genotyping and FU dosing have been published [9] as well as for DPD phenotyping [1]. More importantly, French Health authorities (INCa and HAS) have recently taken position in this DPD-FU arena by issuing a recommendation concerning the determination of plasma uracil before FU administration (https://www.e-cancer.fr, INCa-HAS-Recommandations Nationales FU-DPD).

Thus, clinicians are confronted with the need to evaluate the risk of DPD deficiency before starting FU-based therapy. This situation generates costs and delays prior to start treatment. For instance, a recently published cost analysis of upfront *DPYD* genotype-based dose individualization concluded that this strategy contributed to cost-savings although the net saving was relatively meager [10]. Surprisingly, on the other hand, the impact of DPD deficiency screening in terms of delays in FU-based treatment was not taken into consideration [1,9]. These significant delays (2–3 weeks) can be potentially prejudicial particularly in cases of evolving disease. Thus, given the rather complicated situation of the current FU-DPD testing lock, one can legitimately wonder about possible alternatives. Such alternatives may exist in analytical terms and treatment options.

Regarding DPD testing, development efforts should be steered towards the so-called point-of-care (POC) tests. A POC test, such as the classic urine pregnancy test, has clearly demonstrated its usefulness and practicability. Similarly, an urine-based DPD screening through uracil determination could be simple, cheap, rapid and easy to perform [11]. The underlying aim

E-mail address: gerard.milano@nice.unicancer.fr.

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would be to screen patients and identify the roughly 5% of the population with a positive colorimetric screening test requiring confirmation by means of conventional DPD phenotyping and/or genotyping.

On the other hand, there are treatment options involving fluoropyrimidines in a context which totally or partially eliminates the potential detrimental impact of DPD. In this respect, the oral drug TAS-102 (trifluridine-tipiracil) could offer a useful option since the main active compound (trifluridine) is a fluorinated pyrimidine which, like FU, disrupts in DNA integrity, leading to its dysfunction and antitumoral effect [12]. Nevertheless, unlike FU, trifluridine is not at all subject to catabolism by DPD. TAS-102 has recently proven its clinical activity in advanced colorectal cancer, a priority domain of FU [13]. Alternatively, FU oral drugs like S-1 which incorporates a DPD inhibitor (facilitating oral drug bioavailability) may be markedly less impacted by DPD deficiency. S-1 is in fact already placed in a context of DPD inhibition and thus it will be less affected by a more or less profound DPD deficiency as compared to the impact on a conventional iv or oral FU. Supporting this view, much less cardiac toxicity has been reported under TAS-102 or S-1 as compared to conventional FU therapy [14]. The authors attributed this observation to the reduced formation of the cardiotoxic FBAL generated through DPD.

To conclude, the current medical and legal context are generating a close link between FU treatment initiation and DPD testing. This entails costs and delays and significantly complicates FU treatment for both patients and treatment staff. It is thus advisable to consider possible alternatives. These may result from a rapid and easy DPD testing solution designed like a POC test or from FU-based treatment with oral drugs like TAS-102 and S-1 which totally or partially eliminate the deleterious impact of DPD deficiency.

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