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Review

Prospective *DPYD* genotyping to reduce the risk of fluoropyrimidine-induced severe toxicity: Ready for prime time

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Abstract 5-Fluorouracil (5-FU) and capecitabine (CAP) are among the most frequently prescribed anticancer drugs. They are inactivated in the liver by the enzyme dihydropyrimidine dehydrogenase (DPD). Up to 5% of the population is DPD deficient and these patients have a significantly increased risk of severe and potentially lethal toxicity when treated with regular doses of 5-FU or CAP. DPD is encoded by the gene *DPYD* and variants in *DPYD* can lead to a decreased DPD activity. Although prospective *DPYD* genotyping is a valuable tool to identify patients with DPD deficiency, and thus those at risk for severe and potential life-threatening toxicity, prospective genotyping has not yet been implemented in daily clinical care. Our goal was to present the available evidence in favour of prospective genotyping, including discussion of unjustified worries on cost-effectiveness, and potential underdosing.

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We conclude that there is convincing evidence to implement prospective *DPYD* genotyping with an upfront dose adjustment in DPD deficient patients. Immediate benefit in patient care can be expected through decreasing toxicity, while maintaining efficacy.

Case: fatal toxicity following treatment with capecitabine

A 52-year-old woman with human epidermal growth factor receptor 2 (HER2)-positive metastasised breast cancer was treated with capecitabine 1250 mg/m^2 twice daily, for 14 d every 3 weeks, plus intravenous trastuzumab on day 1. The first cycle was fully completed; at day 18 of treatment mild diarrhoea and a herpes zoster infection located at her mouth were noticed during routine outpatient visit. Due to low haematological laboratory values (leucocytes, neutrophils CTC grade II, and thrombocytes CTC grade III), the second cycle was planned to be deferred by 1 week. However, 3 d later she returned to the hospital with now severe diarrhoea (CTC grade IV), sepsis, neutropenic fever, severe leucopenia and life-threatening thrombocytopenia and mucositis, for which she was admitted to the intensive care unit. A long and intensive hospitalisation period followed, but despite optimal treatment and supportive care, the patient did not recover from severe toxicity and deteriorated even further. At day 34 of admission the patient deceased as a result of this severe toxicity. Genetic testing revealed that the patient was heterozygous for *DPYD**2A, a variant allele known to result in dihydropyrimidine dehydrogenase deficiency [1]. In case screening would have been performed prior to start of therapy, capecitabine dosage could have been reduced by 50%, thereby possibly preventing fatal capecitabine-induced toxicity [2].

1. Introduction

5-Fluorouracil (5-FU) and its oral pro-drug capecitabine (CAP) belong to the group of the fluoropyrimidine drugs, and are among the most frequently used anticancer drugs in the treatment of common cancer types such as colorectal, stomach, breast, head and neck and skin cancer [3–7]. 5-FU has a relatively narrow therapeutic index and, depending on type of treatment regimen, around 15–30% of patients suffer from severe toxicity such as diarrhoea, nausea, mucositis, stomatitis, myelosuppression, neurotoxicity and hand-foot syndrome [4,8–12]. These side-effects lead to mortality in approximately 0.5–1% of patients using 5-FU and CAP [4,13].

The enzyme dihydropyrimidine dehydrogenase (DPD) plays a key role in the catabolism of 5-FU. It is the rate limiting enzyme degrading over 80% of the drug to its inactive metabolite 5-fluoro-5,6-dihydrouracil [9,14,15]. Because of this, DPD is an important factor for efficacy [16,17], as well as the development of toxicity [10]. DPD is encoded by the gene *DPYD*, which consists of 23 exons on chromosome 1p22 [18]. More than 160 single nucleotide polymorphisms (SNPs) are known within this gene, some resulting in altered enzyme activity [19]. Eighty *DPYD* variants were experimentally tested for their enzyme activity [20] and *DPYD* variants may result in an absolute or a partial DPD-deficiency (0.5% versus 3–5% of the population, respectively) [21,22]. About 30–50% of the patients treated with a fluoropyrimidine drug who suffer from severe or life-threatening toxicity (grade III–V) have no or decreased DPD enzyme activity, and 50–88% of patients carrying a variant in *DPYD* suffer from grade ≥III fluoropyrimidine-related toxicity [6,10,11,21,23–25].

Although pharmacogenomic tests in general have the potential to improve clinical outcome by increasing efficacy and decreasing toxicity, and the potential to decrease the cost of health care, their use in routine clinical practice is still limited [26]. This also holds true for the use of *DPYD* genotyping prior to start of treatment with fluoropyrimidines [27,28]. Other DPD deficiency screening methods (e.g. phenotyping) have been described [29], and are currently being investigated (NCT02324452), but we feel are not ready yet for clinical application. In the current paper, we present an overview on the evidence for prospective *DPYD* genotyping and discuss critical questions related to its implementation. Associations of *DPYD* variants with fluoropyrimidine-induced toxicity, prevention of severe toxicity upon *DPYD* testing, cost consequences and existing guidelines will be discussed.

2. Available evidence for the association of *DPYD* variants and 5-FU-induced severe toxicity

The relationship between *DPYD* variants and 5-FU-induced severe toxicity is widely acknowledged. Recently, data have been summarised in three separate meta-analyses [8,9,30]. Terrazzino *et al.* evaluated 4094 patients (15 studies) for *DPYD**2A (IVS14+1G>A; rs3918290) and 2308 patients for c.2846A>T (D949V, rs67376798). They confirmed the clinical validity of these SNPs as risk factors for the development of fluoropyrimidine-associated severe toxicities (details in