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Editorial Open Access

Revisiting the Clinical Importance of DPYD*9A (c.85T>C) Variant of Dihydropyrimidine Dehydrogenase (DPYD) Gene in Patients Treated with Fluoropyrimidine-Based Chemotherapy

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Editorial

Gastrointestinal toxicity due to chemotherapeutic drugs is a common problem in cancer patients. Chemotherapy-related diarrhea is most commonly described with fluoropyrimidines (fluorouracil and capecitabine) and irinotecan. Fluoropyrimidines are widely used for the treatment of gastrointestinal (GI) tract tumors and also in other solid malignancies such as breast and head and neck cancers [1,2] and are relatively well tolerated, however, around 5% to 10% of the treated patients develops severe, potentially life threatening toxicity such as GI toxicity, skin toxicity, myelosuppression and neurotoxicity [3]. Early identification of patients at risk of developing fluoropyrimidines-induced toxicity by upfront screening might allow dose reduction or selection of an alternative chemotherapy regimen. The two well-studies predictive markers for fluoropyrimidines-related toxicity are dihydropyrimidine dehydrogenase (DPD) and thymidylate synthase (TS) enzymatic activity.

The DPD is a rate-limiting enzyme out of three enzymes in fluoropyrimidine metabolic pathways. The partial or complete deficiency of DPD activity has been shown to increase severe or fatal toxicity. To date, over 128 mutations and polymorphisms in DPD encoding gene (DPYD) has been reported [4,5]. Among those, 3 variants (DPYD*2A, DPYD*13 and DPYD*9B) have been shown to be associated with reduced DPD activity and thus enhanced toxicity in patients treated with fluoropyrimidine-based chemotherapy. Some research group also reported the suppressed activity due the aberrant methylation of the DPYD promoter region acted as one of the repressors of DPYD expression at transcriptional level and affected sensitivity to 5-FU in cancer cells [6,7].

The correlation between DPYD*9A (c.85T>C) genotype and DPD deficiency clinical phenotype is controversial [8,9]. In some studies, in patients with GI malignancies, DPYD*9A (c.85T>C) variant was associated with fluoropyrimidines-associated toxicity. Patients experienced diarrhea ($p<0.05$) and hand foot syndrome (HFS) ($p<0.05$) [8,10,11]. Other clinical studies reported that there is no correlation between DPYD*9A (c.85T>C) genotype and DPD deficiency clinical phenotype. Based on the current limited knowledge, the 2017 updated Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for DPD genotype and fluoropyrimidine dosing, it was stated that the DPYD*9A (c.85T>C), among other variants, doesn't affect DPD activity in a clinically relevant manner [12-14]. So, the reference laboratories either did not perform DPYD*9A genotyping or have stopped DPYD*9A genotyping and limited genotyping to high-risk variants (DPYD*2A, DPYD*13 and DPYD*9B) only.

Recently, our group has reported that DPYD*9A (c.85T>C) variant was the most common variant diagnosed in our cohort and a genotype-clinical phenotype correlation was noticeable. All patients who received full dose fluoropyrimidines experienced grade 3-4 diarrhea [15,16]. Other group have also reported the correlation between DPYD*9A (c.85T>C) and grade 3-4 toxicity [8,10,11]. Moreover, the Li et al. [17] reported that the (DPYD*9A T/T and T/C genotypes accounted for 85.7% and 14.3% in colorectal cancer, respectively and correlated with the toxicity [17]. These finding indicate the importance of genotyping of this variant to avoid the fluoropyrimidine-related toxicity and need to be considered upfront along with other high risk variants.

Fluoropyrimifines-related toxicity not only results in treatment interruption but also sometimes discontinuation, adversely affecting the quality of life and an increase in health care cost. Up front screening of DPD deficiency through genotyping for high-risk DPYD variants (DPYD*2A, *13 and *9B) only is suboptimal to predict fluoropyrimidine-related toxicity. Genotyping for DPYD*9A in addition to the high-risk DPYD variants represents a more comprehensive approach. Diagnosing of DPD deficiency upfront provide the treating oncologist the opportunity to avoid fluoropyrimifines-related toxicity. In patients who are heterozygous, oncologists are advised to start their patients on a reduced dose with subsequent titration or choosing an alternative regimen. In patients who are homozygous, fluoropyrimidines-based regimen should be avoided.

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Conflict of Interest

The authors have no conflicts of interest to disclose.

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