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DIHYDROPYRIMIDINE DEHYDROGENASE VARIANTS OF CLINICAL IMPORTANCE AND DOSE ADJUSTMENT PRACTICES

[1]**Ranadeep Gogoi,** [1]**Maihur Basumatary,** [2]**Neelakshi Mahanta,** [3]**Devajit Choudhury**

[1]Consultant, [1]Application Scientist, [2]Professor & HoD, [3]Associate Professor & Superintendent

[1]Molecular Oncology Laboratory, State Cancer Institute, GMC, Guwahati-781032, Assam, India
[2]Medical Oncology, State Cancer Institute, GMC, Guwahati-781032, Assam, India
[3] Surgical Oncology & Superintendent, State Cancer Institute, GMC, Guwahati-781032, Assam, India

Abstract: This review discusses the significant role of Dihydropyrimidine dehydrogenase (DPD) in cancer drug metabolism, causing severe toxicity. It highlights that 71% of severe 5-Fluorouracil (5-FU) toxicity patients have reduced DPYD activity, contributing to adverse effects. The four variant genes DPYD*2A, DPYD*13, SNP c.2846A>T, and HapB3 are significant contributors to adverse events, accounting for at least 20% of severe toxicities associated with 5-FU. The review suggests pre-emptive screening for DPYD variants and genotype-guided dose adjustments to improve patient safety.

Key words: Dihydropyrimidine Dehydrogenase (DPYD), Gene Mutation, 5-Fluorouracil, Genotype-guided dose

INTRODUCTION

Cancer rates worldwide reached 29.5 million annually in 2040, with 16.4 million deaths. High life expectancy, education, and living standards contribute to higher rates.[1] The Dihydropyrimidine Dehydrogenase enzyme, essential for cancer drug metabolism, increases drug content and toxic effects.[2] DPD is represented in peripheral blood mononuclear cells (PBMCs) using the DPYD gene, influenced by transcription and translation processes with transcription factors like SP1, SP3, and microRNA-27a and 27b.[3]

Gene mutations can affect the DPD enzyme, causing increased toxicity and varying functional forms of fluoropyrimidine.[4] This enzyme affects tumor growth and medication responsiveness, and can be influenced by alcoholism and smoking.[5]Sex also affects drug metabolism, with women experiencing lower clearance and 3%-8% experiencing DPD deficiency due to DPYD polymorphisms.[6] The 5-Fluorouracil drug, used in cancer treatment since 1962, caused the first toxicity case in 1985.[7] The European Medicines Agency (EMA) advises patients with DPD enzyme deficiency to be tested before using 5-fluorouracil medication to prevent life-threatening issues, and therapeutic drug monitoring can improve patient conditions.[8]

DPD enzyme activity:

Determining DPD deficiency in patients involves analyzing uracil concentration or dihydrouracil in peripheral blood mononuclear cells.[9] DPD enzyme activity detection is achieved through DPYD genotyping using DHPLC performance liquid chromatography.[10] DPD enzyme activity is higher during fasting and decreases after food intake. Diagnostic tests help predict patients at risk of 5-fluorouracil treatment due to DPD enzyme deficiency.[11]

DPD phenotyping measures enzyme activity and determines DPD deficiency. It involves four tests: enzyme activity, endogenous uracil and dihydrouracil levels, Uracil breath test, and Uracil test dose. Age affects pharmacokinetics, and adverse drug reactions are common in individuals with less than 70% DPD activity. DPD deficiency cancer patients should use non-fluoropyrimidine regimens and undergo DPYD variant tests before starting 5-fluorouracil treatment. Four variant genes, DPYD*2A, DPYD*13, SNP c.2846A>T, and HapB3, contribute to 20% of severe toxicities associated with 5-FU treatment.[12] DPYD deficiency alters metabolism and causes adverse medication reactions.[13] US oncology guidelines recommend testing for all 5-FU patients.[14]

Clinical Prevalence of DPYD deficiency:

Studies showed that 71% of severe 5-FU toxicity patients have reduced DPYD activity, contributing to adverse effects. Controlling toxicity can be achieved by reducing 5-FU dose or using uridine triacetate.[15] DPYD deficiencies are prevalent in Caucasian and African-American populations (3-5% and 8% respectively), but their prevalence in the Indian population remains unknown.[16] In India, 32.4% of advanced head and neck cancer patients have a DPD mutation, suggesting that mutation status may vary based on region and ethnicity.[17]

A study of 157 individuals found 23 DPYD gene variants, with 15 common haplotypes. Rare mutations and novel point mutations varied DPD enzyme activity.[18] Another study found eight DPYD polymorphisms associated with Grade ≥3 toxicity in 603 cancer patients treated with fluoropyrimidines. 57% of patients needed dose or schedule modifications for moderate chronic toxicity.[19]

A retrospective pharmacogenetic study found that 10 DPYD variants were associated with fluoropyrimidine-related adverse events.[20]Another study also identified 22 unique variants in 50 healthy Indians, six of which were not previously documented.[21] A study in Ecuador found that 20-30% of fluoropyrimidine patients experience severe toxicity due to molecular variants in the DPYD gene. The genetic variability in the DPYD gene is related to ancestral populations in different Ecuadorian ethnic groups, with the absence of variants with predictive value for fluoropyrimidine toxicity.[22]

A study found that African-Americans, particularly women, have reduced peripheral blood mononuclear cell DPD enzyme activity, potentially increasing their risk of 5-FU toxicity.[22] A RT-PCR technique detected DPYD*2A in Kurdish patients receiving fluoropyrimidine derivatives, causing adverse drug reactions.[23] A study in India confirmed partial DPD deficiency through radioassay measurement. An oral UraBT assay was developed to detect DPD deficiency in cancer patients before 5-FU administration.[24] Retrospective studies and meta-analyses confirm an increased risk of toxicity related to fluoropyrimidine treatment in DPYD*2A variant allele carriers.[25-26]

DPYD Gene and variants:

Dihydropyrimidine dehydrogenase is a crucial enzyme in the catabolism of pyrimidines, and complete or partial loss of DPD function has been reported in cancer patients with intolerance to fluoropyrimidine drugs like 5-fluorouracil (5-FU) or Xeloda. Four DPYD variants, c.1905+1G>A (rs3918290, also known as DPYD*2A), c.1679T>G (rs55886062, DPYD *13), c.2846A>T (rs67376798), and c.1129–5923C>G (rs75017182, HapB3) are significant in 5-fluorouracil, impacting enzyme function and toxicity risk. Europeans carry approximately 7% of these variants, while African ancestry individuals often carry the variants. Tests for 5-fluorouracil toxicity primarily focus on these risk variants.

Individuals with a no-function DPYD variant may carry an inborn metabolism error, affecting offspring. Patients homozygous for inactivating DPYD have complete dihydropyrimidine dehydrogenase deficiency. The clinical utility of TYMS and MTHFR gene variants in testing 5-fluorouracil toxicity is unclear, and predictive dosing strategies have not been successfully applied.[19] Pre-emptive screening for DPYD variants and genotype-guided dose adjustments can improve patient safety. Severe fluoropyrimidine-related toxicity is influenced by interindividual variability in DPD activity, with an estimated 3%-8% of the population being partially deficient.

DPYD*2A is a polymorphism in DPYD, leads to skipping of the entire exon 14 and deletion of 165 base pairs causing a truncated protein with inactive catalytic activity.[27] It is associated with decreased DPD enzyme activity in PBMCs and liver activity. Allele frequencies vary between African-American and Caucasian populations. Additional variants associated with DPD deficiency have been identified.[28]

The c.2846A>T variant allele disrupts the DPD enzyme, affecting cofactor binding and electron transport. In vitro data shows a 59% decrease in activity compared to wild-type, but not as severe as DPYD*2A. This suggests that a heterozygous carrier would have a 25% reduction in DPD activity and benefit from a 25% dose reduction.[29]

The rare DPYD variant c.1679T>G results in a 75% reduction, and the c.1236G>A polymorphism linked to haplotype B3 (HapB3), of which c.1129-5923C>G intronic polymorphism affects DPD enzyme activity in Caucasian patients. A 25% dose reduction is recommended for heterozygous carriers.[30]

A systematic review and meta-analysis by Meulendijks et al. found that DPYD variants c.1679T>G, c.1236G>A, and c.2846A>T are clinically relevant predictors of fluoropyrimidine-associated toxicity in 7356 patients.[31] A study analyzing over 3000 south Asians found significant differences in allelic distribution of variants across different ethnicities.[32] A study screened 2000 Indian subjects for DPYD variants using the Infinium Global Screening Array identified seven coding, two intronic, and three synonymous DPYD variants.[33] The study also found that the IVS14+1G>A mutation in the DPD gene is associated with severe DPD deficiency, making genetic screening useful before 5-FU administration in the Indian breast cancer population.[33]

Fluoropyrimidine-based dose optimization:

Initial dose reductions for heterozygous carriers of three DPYD polymorphisms, as well as DPYD*2A carriers, should normalize 5-fluorouracil exposure and reduce severe toxicity risk. A prospective clinical trial found that genotype-guided dosing for DPYD*2A variant allele carriers had a significantly lower risk of severe treatment-related toxicity and reduced drug-related death from 10% to 0%. Patients were genotyped for DPYD*2A and received an initial dose reduction of 50%.[34] The Clinical Pharmacogenetics Implementation Consortium recommends initial dose reductions for DPYD variants c.2846A>T and c.1679T>G, including DPYD*2A.[35] Individual dose up titration can be applied for maximum safe exposure. DPYD genotyping and individualized dosing can reduce toxicity incidence, potentially decreasing healthcare costs.[34] The US oncology guidelines recommend DPYD testing for all patients requiring treatment with 5-fluorouracil, irinotecan, and capecitabine.

The review discusses the molecular basis of 5-fluorouracil toxicity, focusing on DYPD deficiency. Partial DYPD deficiency is common, with a prevalence of 3-5% in the general population and 12% in African-American females. Over 50 genetic polymorphisms are associated with decreased enzymatic activity, with the c.1905+1G>A point mutation being the most common. Cardiotoxicity associated with 5-FU or capecitabine is estimated to be 1.2-8%. [36] A study found that rs75017182 may have clinical utility as a predictor of 5-FU toxicity.[37] DPD-deficient cancer patients are at risk for severe myelosuppression,[38] and DPD deficiency may increase 5-FU half-life and severity of toxicities.[39] Dose reduction in DPD deficient patients reduces life-threatening complications, but not completely. Health authorities are encouraged to adjust capecitabine and 5-FU labels and pre-emptive DPYD genotyping and dose individualization to improve fluoropyrimidine therapy safety.[34,40] The study found that patients with DPYD mutations can manage drug toxicity by reducing the dose of 5-FU or using uridine triacetate, an FDA-approved antidote, which may protect them from adverse drug events.[41]

Conclusion:

DPD deficiency can cause toxicities like mucositis, granulocytopenia, diarrhea, and neuropathy, potentially leading to death if undiagnosed. Further research is needed to identify at-risk populations to understand the epidemiological incidence of DPD deficiency among ethnic and racial groups, as 5-FU remains the third most commonly used chemotherapy globally. This review emphasizes the need for pre-emptive screening for DPYD variants and genotype-guided dose adjustments in the new standard of care to enhance patient safety.

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ABBREVIATIONS:
DPD: Dihydropyrimidine dehydrogenase; 5-FU: 5-Fluorouracil; EMA: European Medicine Agency; DPYD: Gene encoding DPD; PBMCs: Peripheral Blood Mononuclear cells; DHPLC: Denaturing high resolution chromatography

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