Allelic frequency of DPYD genetic variants: implementation of a genotyping test in Mexican population

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Background: Fluoropyrimidine-based (FP) chemotherapy is extensively used to treat solid cancers, including colorectal and breast cancer. A dihydropyrimidine dehydrogenase (DPD) enzyme deficiency, encoded by the dihydropyrimidine dehydrogenase (*DPYD)* gene, increases the risk of severe toxicity. FP toxicity affects about 30-40% of patients, which in some cases may be lethal. FPs have been used for over 50 years, and an estimated 2 million cancer patients are treated with FP drugs annually. In particular, FPs remain among the most effective drugs for treating GI malignancies, including colorectal cancer (CRC) (1.8 million), gastric (1 million), and pancreatic cancer (n=460,000). In Mexican oncology practice, FP and capecitabine chemotherapies are the most common drugs for gastrointestinal, head and neck, and breast tumors. *DPYD* genotyping aims to identify variants that lead to DPD deficiency. We implemented a seven-allelic genotyping test and analyzed the frequency in the Mexican population.
Methods: We included seven *DPYD* variants: c.1129-5923C->G, c.2846A->T associated with increased risk toxicity (reduced activity), and c.1156G->T, c.1905+1G->A, c.1679T->G, c.1898delC, and c.299_302delTCAT associated with high risk for FP toxicity (no activity or significantly reduced activity). Genomic DNA was isolated from 280 subjects: 36 cancer patients and 244 non-cancer subjects. We analyzed *DPYD* variants by real-time PCR (c.1156G->T, c.2846A->T, and c.1129-5923C->G) and Sanger sequencing (c.1905+1G->A, c.1679T->G, c.1898delC and c.299_302delTCAT) The allele frequency was calculated for each variant.
Results: For Sanger sequencing, primers were designed to amplify four variants. Amplified products of the expected size were obtained. Three variants were amplified using TaqMan probes and synthetic positive controls for both alleles. We found the c.1129-5923C>G variant in the heterozygous state in 1% (n= 3), and the c.2846A>T variant was found in 0.33% (n=1) of the participants. We did not found the rest of the variants in the Mexican population.
Conclusions: The allele frequency for two of the seven analyzed variants (c.1129-5923C->G and the c.2846A>T) was higher than reported for the global population (0.00476, and 0.005166). DPYD genotyping may help identify patients at higher risk of developing severe FP toxicity. Personalized medicine allows oncologists to modify the treatment before it begins.