DETERMINATION OF GENETIC POLYMORPHISMS OF THE DIHYDROPYRIMIDINE DEHYDROGENASE GENE IN REAL CLINICAL PRACTICE AS PREDICTORS OF SEVERE FLUOROPYRIMIDINE-ASSOCIATED TOXICITY.

Alvarado Fernández, MD; Rendón de Lope, L; Villalobos Torres, L; Marcos Rodríguez, JA; Castillo-Martín, C; Murillo Izquierdo, M.
Hospital Universitario Virgen Macarena, Seville, Spain.
Hospital Alto Guadalquivir, Jaén. Spain.

Background

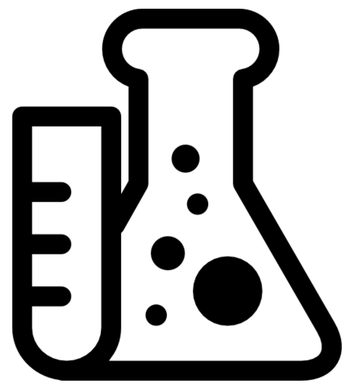
Fluoropyrimidines are antineoplastic drugs used for the treatment of many types of solid tumors. Approximately 80-90% administered is metabolized by the enzyme dihydropyrimidine dehydrogenase (DPYD).
The partial or total deficiency of this enzyme is related to severe toxicity and in some cases it can cause the death of the patient.

Purpose

The aim of our study is to determine the frequency of these polymorphisms in the DPYD gene in patients treated in our hospital and identify those patients with predisposition to excessive toxicity if they are exposed to fluoropyrimidines.

Material and methods

The genetic analysis of the DPYD gene was performed on all patients who started treatment with fluoropyrimidines between september 2017 and april 2020. The variables collected were: age, type of tumor diagnosed and toxicity presented in the first six treatment cycles according to the CTCAE (Common Terminology Criteria for Adverse Events) classification. Data was obtained by the electronic medical record (Diraya®) and the electronic prescription program (Farmis®).



The polymorphisms studied were rs3918290, rs55886062, rs67376798, rs56038477.

Results

The genetic analysis was performed on 171 patients. The median age was 71 years.

Most of the diagnoses correspond to colorectal cancer (81%). The patients presented the following adverse events: digestive toxicity in 59% of patients (CTCAE:1,2,3), mucositis 20% (CTCAE: 1,2), haematological toxicity 17% (CTCAE:2), hepatotoxicity 6%(CTCAE:2, 3), neuropathy 16% (CTCAE:1,2) and erythrodysaesthesia 10% (CTCAE:1,2,3).

42% of patients required drug withdrawal or dose reduction due to the toxicity presented.

Regarding the results of the polymorphisms studied, 95,3% presented a wild-type genotype for the analyzed variants. 4,7% patients presented some mutated allele (heterozygote): three patients for rs3918290, three patients for rs67376798 and two patients for rs56038477 coinciding with the patients who presented greater toxicity.

Conclusions

The heterozygous patients detected are at risk of developing severe toxicity when they are treated with fluoropyrimidines and they required a dose adjustment of these drugs.

The use of these pharmacogenetic tools for the determination of polymorphisms of the DPYD gene in routine practice allows us to predict the potentially serious toxicity favoring the individualized use of these drugs.

VIE21-0301 ATC: L01 Cytostatics

eahp european association of hospital pharmacists