4CPS-230

IDENTIFICATION OF RARE DPYD VARIANTS ASSOCIATED WITH TOXICITY TO FLUOROPYRIMIDINES IN A CLINICAL PHARMACOGENOMICS PROGRAMME

Revuelta JL, García X, Salvador S, Zapata P, Salvador S, Taladríz I, López L, Herranz A, Sanjurjo M
Hospital General Universitario Gregorio Marañón, Pharmacy Department
Instituto de Investigación Sanitaria Gregorio Marañón (IiSGM)

BACKGROUND AND IMPORTANCE

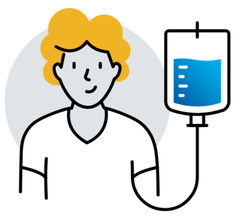
Dihydropyrimidine dehydrogenase (DPYD) is a key enzyme in the metabolism of fluoropyrimidines (5-fluorouracil, capecitabine). Patients with deficiency in DPYD are in great risk of severe adverse events when treated with fluoropyrimidines. Although patients are screened for the most common variants, some develop serious toxicities.

AIM AND OBJECTIVE

A Clinical Pharmacogenomics Program targeted to patients who developed toxicity with fluoropyrimidines was implemented.

We report rare variants in the DPYD gene associated with severe toxicity.

MATERIALS AND METHODS



DPYD sequencing → Identification of variants associated with toxicity

- ✓ Treatment recommendations
- ✓ Patient counselling
- ✓ Development of new test

Patients who suffered severe toxicities (grade≥3 as per CTCAE) during their first three cycles of treatment with fluoropyrimidines were identified by their oncologist or oncology pharmacist. They were all negative for the four recommended variants (DPYD*2A, c.2846A>T, c.1679T>G, and c.1236G>A). Complete sequencing of the 23 DPYD exons was performed in these patients.

RESULTS

- Since 2017, 91 patients have been included in the program.
- 32 variants in DPYD have been identified.
- 9/32 were associated with severe toxicity (table 1).
- This clinical pharmacogenomics program helped found the cause of toxicity in 10% (9/91) of patients.

Table 1. Identified variants in *DPYD* correlated with toxicity.

Variant	DPYD deficiency	Association with increased toxicity
c.257C>T	+	+
c.704G>A	+	+
c.775A>G	+	+
c.851G>T	+	+
c.1977-1984-CTCCAGAA>C	+	+
c.2087G>A	?	+
c.2197insA	+	+
c.2242+1G>T	+	+
c.2324T>G	+	+

Results were discussed with the Oncology team and treatment adjustment recommendations were provided. Patients were also informed of the findings.

CONCLUSION AND RELEVANCE

- Uncommon variants in the *DPYD* gene that were associated with toxicity to fluoropyrimidines were identified with this clinical pharmacogenomics program.
- These variants can be further included in extended screening programs for patients treated with fluoropyrimidines.

joseluis.revuelta@salud.madrid.org @farma_gregorio www.madrid.org/hospitalgregoriomaranon/farmacia