Research Article
Open Access
CrossMark

Personalized therapy: the crucial role of the DPYD c.2194G>A (V732I) allele in the treatment of colorectal cancer patients candidates for therapy with fluoropyrimidines

Abstract

5-Fluorouracil (5FU) is a chemotherapeutic agent belonging to the class of antimetabolite drugs, which exert a toxic action causing death of neoplastic cells. 5FU is mostly used as a standard treatment for colorectal cancer; the development of toxicity phenomena is related to the partial or complete deficiency of the enzyme dihydropyrimidine dehydrogenase (DPD), limiting factor of the catabolism of fluoropyrimidines. Only 3-5% of 5-FU is converted to an active metabolite, while 85% of the drug is inactivated by DPD to 5-fluoro-dihydrouracil (5-FDHU). A reduced enzymatic activity of the DPD can be the cause for the presence of adverse drug reactions and toxicity in the patient, with multiorgan involvement, which can sometimes lead to death.

The variants of the DPYD gene recommended by the AIOM (Associazione Italiana di Oncologia Medica)guidelines are: DPYD*2A (IVS14+1G>A, c.1905+1G>A); DPYD*13 (c.1679T>G); DPYD c.2846A>T, D949V; DPYD c.1236G>A (HapB3); DPYD c.2194G>A (V732I).Patients with complete DPD deficiency are at high risk of life-threatening or fatal toxicity and should not be treated with fluoropyrimidines, but this is a rare condition; while patients with partial deficiency should be treated with a reduced dose of the drug. Before starting treatment it's crucial to determine the genetic profile of the patients candidates to therapy with fluoropyrimidines. In our cohort of the 370 samples analyzed by Real Time PCR, 294(~80%) are wild type for each variant screened. : DPYD c.2194G>A (V732I) alleleis significantly represented in the population examinated: considering the 15% reduction in drug administration imposed by this genotype, molecular profiling is essential before starting therapy with 5FU.In our study we also found a rare variant DPYD F632F rs17376848 c.1896 T> C in a patient, whose relevancefor therapeutic purposes is currently of uncertain significance.

Keywords: 5FU, gene DPYD, DPD, DPYD V732I, DPYD* 2A, rs17376848

Volume 7 Issue 1 - 2022

Pepe N, Maddaloni V, Perfetti A, Macrì A, De Pompeis S, Di Clemente L, Genco L, Rossi S, Boenzi R

Laboratorio di genomica molecolare, UOC Biochimica Clinica Azienda Ospedaliera dei Colli Monaldi-Cotugno-C.T.O.,V. L. Bianchi, Napoli, Italy

Correspondence: Maddaloni V, Laboratorio di genomica molecolare, UOC Biochimica Clinica Azienda Ospedaliera dei Colli Monaldi-Cotugno-C.T.O.,V. L. Bianchi, Napoli, Italy, Tel +390817062531, Email valeria.maddaloni@gmail.com

Received: September 26, 2022 | **Published:** October 03, 2022

Introduction

Numerous genetic conditions have been identified that decrease the metabolism of chemotherapeutic agents and therefore increase the toxicity of anticancer drugs.

Fluoropyrimidines are used as treatment of many solid tumors, but several adverse effects of fluoropyrimidines are known:they can cause neutropenia, neurotoxicity, heart conduction compromission ad other less critical simptoms. In a small sample of threated patients (less than 1%) the death is a described effect[1] 5-fluorouracil (5FU) is a chemiotherapeutic agent, mostly used as a standard treatment colorectal cancer.

5FU is a drug of considerable importance and for this reason it has been included in the list of essential drugs drawn up by the World Health Organization. It causes toxicity phenomena due to partial or total deficiency of the enzyme dihydropyrimidine dehydrogenase (DPD). This enzyme produced by the *DPYD* gene (chr 1), is a limiting factor in the catabolism of fluoropyrimidines. Reduced enzymatic activity of DPD can lead to multi-organ damage, sometimes causing death. It acts as an analogue of uracil, interrupting the synthesis of nucleic acids.

The *DPYD* gene is highly polymorphic: numerous allelic variants have been identified, there are variants that produce the protein in a truncated form with significantly reduced enzymatic activity. A significant part of the Caucasian population has low levels of a working DPD enzyme (up to 9%), while up to 0.5% completely lack the enzyme. The variants of the *DPYD* gene recommended by majoroncological guidelines[2-4] are: DPYD*2A, DPYD*13, D949V, DPYD HapB3, and only recently the V732I variant, that isn't included in all commercial and validated kits for DPYD screening. Here we illustrate how the introduction of this new variant in the DPYD gene screening modified the approach to the patient, since it's more present in our cohort respect other variants.

Materials and methods

The study was carried out on 370 cancer patients enrolled by 2018 until September 2022 in AORN OspedalideiColli, Monaldi-Cotugno-CTO hospital, Naples, Italy. Tests were performed on gDNA from patients peripheral blood samples, the informed consent was also collected for each patient enrolled. The Real Time test was performed byLightCycler® Roche Diagnostics system using primers and probes by TIBMOLBIOL-Roche® in combination with Cobas z 480 (Roche®).

Results

In the population examined, 294 of 370 (80%) are wild type for all the variants screened. Results are listed in the table 1. It was important to verify that the DPYD V732I variant is frequently found in heterozygosis (14%) (Table1).

Table 1 Results from the cohortscreened

	Wild type n. %	Heterozygotes n. %
DPYD*2A (IVS14+1G>A, c.1905+1G>A)	361	8
	97.8	2.2
DPYD*13 (c.1679T>G)	369	1
	99.7	0.3
DPYD c.2846A>T, D949V	367	3
	99.2	0.8
DPYD c.1236G>A (HapB3)	359	11
	97.03	2.97
DPYD c.2194G>A (V732I)	318	50
	85.95	13.51

Instead, 2 mutated homozygotes were detected for the *DPYD* V732I variant and1rare variant for the DPYD* 2A allele, exon 14, in position c.1896 T> C, rs17376848 (F632F) (Figure 1).[5]

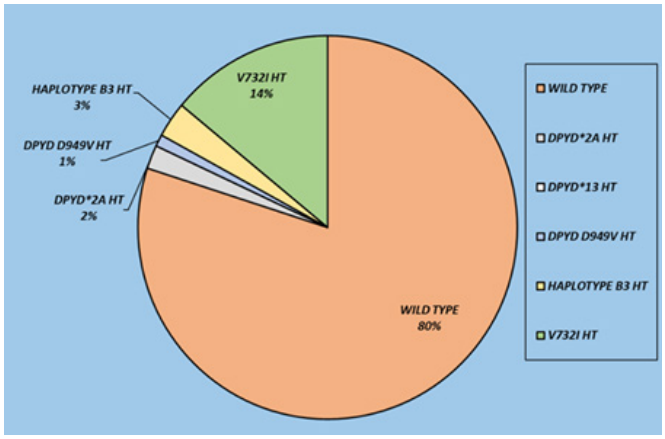

Figure 1 Distribution of DPYD variants in 370 patients. The graph doesn't show percentages lower than 1%.

Discussion

Adverse drug reactions represent a serious clinical problem and are the fourth leading cause of death after heart disease, cancer and stroke. Patients with neoplastic diseases treated with 5-FU may show different degrees of toxicity, that can even be lethal. [6-8] This chemotherapicis usually used for the treatment of patients in whom it is not possible to intervene by surgery.

5FU should be administered under the strict supervision of a specialized medical staff. Since fluorouracil has high toxicity and a low margin of safety, patients should be carefully and constantly monitored during treatment and hospitalization is recommended at least during the initial course of chemotherapy.

Our results highlight that the V732I variant (c.2194 G>A) is more frequently than other variants. Its research is crucial and strongly recommended in case of fluoropyrimidine toxicity during therapy; therefore, it's necessary to include it in all pharmacogenomic tests relating to fluoropyrimidines and consider any reduction in drug's dose to be administered, according to the AIOM,SIF and EMA guidelines(AssociazioneItaliana di Oncologia Medica -Italian Association of Medical Oncology; SocietàItalianaFarmacologia - Italian Pharmacology Society; European Medicine Agency) (Table 2).[2-4]

Table 2 AIOM recommended doses of the drug 5FU[3]

	Genetic variants	c.DNA	The raccomended dosage of Fluoropyrimidines
Wild type	DPYD*2A	c.1905+1 GG	100%
	DPYD*13	c.1679 TT	
	DPYD D949V	c.2846 AA	
	Haplotype B3	c.1236 GG	
	DPYD V732I	c.2194 GG	
Heterozygote	DPYD*2°	c.1905+1 GA	50%
	DPYD*13	c.1679 TG	
	DPYD D949V	c.2846 AT	
	Haplotype B3	c.1236 GA	75%
	DPYD V732I	c.2194 GA	85%
Mutated homozygote	DPYD*2°	c.1905+1 AA	Do not administer fluoropyrimidines
	DPYD*13	c.1679 GG	
	DPYD D949V	c.2846 TT	
	Haplotype B3	c.1236 AA	50%
	DPYD V732I	c.2194 AA	70%

It is also known that some rare variants of the DPYD gene can be associated with an increased risk of toxicity. We found the rare variantrs17376848 (F632F) (DPYD * 2A allele), that is still a controverse variant, its role remain of uncertain clinicalsignificance.[9-11]

Acknowledgments

None.

Conflicts of interest

Author declares that there is no conflict of interest.

References

1. Lamont EB, Schilsky RL. The oral fluoropyrimidines in cancer chemotherapy. *Clin Cancer Res*. 1999;5(9):2289–2296.
2. Boige V, Vincent M, Alexandre P, et al. DPYD genotyping to predict adverse events following treatment with fluorouracil-based adjuvant chemotherapy in Patients with stage III colon cancer: A secondary analysis of the PETACC-8 randomized clinical trial. *JAMA Oncol*. 2016;2(5):655–662.
3. https://www.aiom.it/raccomandazioni-2019-per-analisi-farmacogenetiche/
4. EMA recommendations on DPD testing prior to treatment with fluorouracil, capecitabine, tegafur and flucytosine. *Curr Oncol*. 2020;28:94–97.
5. Palmirotta R, Lovero D, Delacour H, et al. Rare dihydropyrimidine dehydrogenase variants and toxicity by floropyrimidines: A case report. *Front Oncol*. 2019;9:139.
6. de With M Knikman J, de Man FM, Lunenburg CATC, et al. Dihydropyrimidine dehydrogenase phenotyping using pretreatment uracil: A note of caution based on a large prospective clinical study. *Clin Pharmacol Ther*. 2022;112:62–68.
7. Kleibl Z, Fidlerova J, Kleiblova P, et al. Influence of dihydropyrimidinedehydrogenase gene (DPYD) coding sequencevariants on the development of fluoropyrimidine-relatedtoxicity in patients with high-grade toxicity and patients with excellenttolerance of fluoropyrimidine-basedchemotherapy. *Neoplasma*. 2009;56(4):303–316.
8. Pharmacovigilancerisk assessment committee (PRAC). *European Medicines Agencies*; 2020.
9. Etienne-Grimaldi MC, Boyer JC, Beroud C, et al. New advances in DPYD genotype and risk of severe toxicity under capecitabine. *PLoS One*. 2017;12(5):e0175998.

10. Ben Fredj R, Gross E, Chouchen L, et al. Mutational spectrum of dihydropyrimidine dehydrogenase gene (DPYD) in the Tunisianpopulation. *CR Biol.* 2007;330(10):764–769.

11. Kek Tek L, Hanzah S, Hashim H, et al. The - Potential of dihydropyrimidine dehydrogenase genotypes in personalizing 5-fluorouracil therapy among colorectal cancer patients. *Ther Drug Monit.* 2013;35(5):624–630.

Citation: Pepe N, Maddaloni V, Perfetti A, et al. Personalized therapy: the crucial role of the DPYD c.2194G>A (V732I) allele in the treatment of colorectal cancer patients candidates for therapy with fluoropyrimidines. *J Stem Cell Res Ther.* 2022;7(1):18–20. DOI: 10.15406/jsrt.2022.07.00151