Correlation between DPYD gene variants and Fluoropyrimidines-related toxicities: real-world data from a single-center.

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BACKGROUND AND AIMS

Fluoropyrimidines (FPs) are widely used in the standard therapy for various solid cancers, but they can lead to severe Adverse Events (AEs) in a significant proportion of patients, ranging from 10% to 30%.

Dihydropyrimidine dehydrogenase (DPYD) is responsible for metabolizing FPs in the liver, and mutations in the gene can decrease enzyme activity, further increasing the risk for AEs.

This study aims to investigate the prevalence of DPYD-deficient gene variants and their impact on patients undergoing FP-based therapy starting from March 2020 (soon after the publication of EMA/AIFA and AIOM-SIF guidelines) to March 2022.

METHODS

Between 2020 and 2022, we conducted a prospective monocentric study involving a cohort of 505 patients who were potential candidates for FP-based therapy.

Prior to initiating treatment, we performed germline DPYD analysis using a fast and reliable RT-PCR panel of five DPYD variants (according to Italian AIOM-SIF guidelines): IVS10, *13, *2A, D949V, and *6 by «**Diatech Pharmacogenetics *EasyPGX ready DPYD***» totally produced with innovative «dry» reagents format: No need for master mix preparation, hands-on time, high Turn around Time (both for reagents preparation and post PCR analysis), stable at room temperature.

The most common tumor site was the gastrointestinal (n=75; 83.3%), followed by head-neck (n=10; 11.1%), and breast (n=7; 7.7%).

Additionally, we reviewed the patient's medical records to explore any correlations between these mutations, types and grades of AEs.

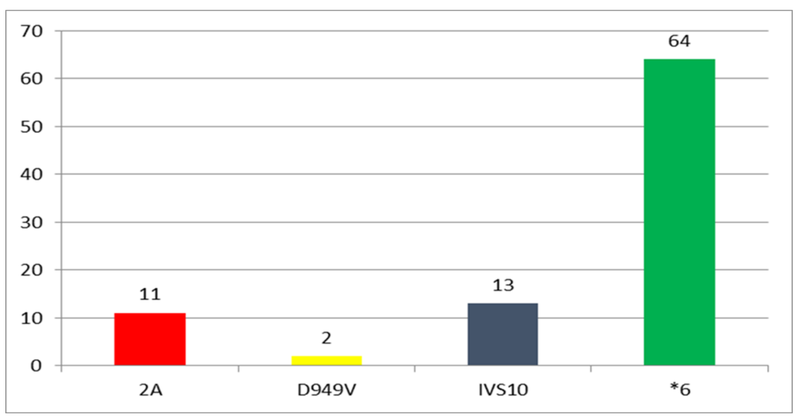
RESULTS: mutation analysis and distribution.

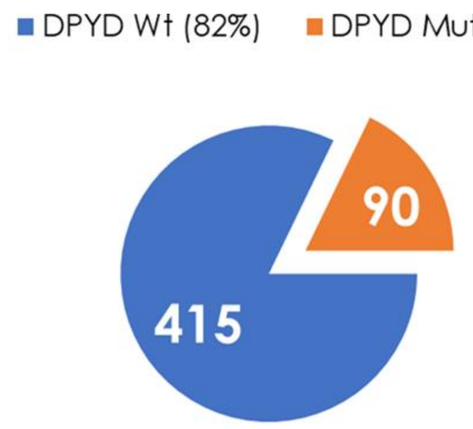
Out of 505 patients genotyped between March 2020 and March 2022, 90 (18%) showed at least one mutation in the DPYD gene.

Overall, 415 patients were DPYD Wt (82%), and 90 (18%) were carriers of a deleterious DPYD variant:

- c.2194GA (*6) was detected in 64 cases (71%),
- IVS10 in 13 cases (14%),
- *2A in 11 cases (12%), and
- D949V in 2 cases (3%).

Of note, *13 mutation was not observed in our cohort.





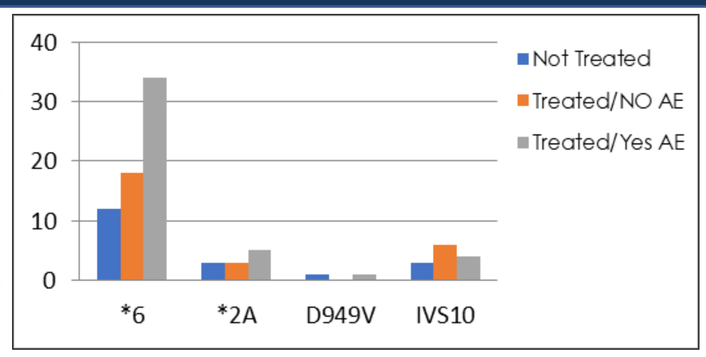
Mutation	dbSNP ID	Gene Position	aa Change	N (%)
DPYD*2A	rs3918290	c.1905+1G>A	IVS14+1G>A	11 (12.2%)
p.D949V	rs67376798	c.2846A>T	p.D949V	2 (2.2%)
IVS10C>G	rs75017182	c.1129–5923C>G	IVS10C>G, HapB3	13 (14.4%)
DPYD*6	rs1801160	c.2194G>A	V732I	64 (71.1%)
DPYD*13	rs55886062	c.1679T>G	p.I560S	0 (not found)

RESULTS: characterstics of the mutated patients.

TOTAL MUTATED PATIENTS (n;%)	90/505; 18%			
GENDER	M 50/90; 55,6%		F 40/90; 44,4%	
TUMOR SITE (n;%)	GI 75/90; 83,3%	Head and Neck 10/90; 11,1%		Breast 7/90; 7,7%
STAGE (AJCC 8TH ED) (n; %)	I: 3/90; 3,3%	II: 13/90; 14,4%	III: 21/90; 23,3%	IV: 56/90; 62,2%

RESULTS:AEs and mutation.

MUT	Not Treated	Treated/NO AEs	Treated/YES AEs	TOT
*6	12	18	34	**64**
*2A	3	3	5	**11**
D949V	1	0	1	**2**
IVS10	3	6	4	**13**

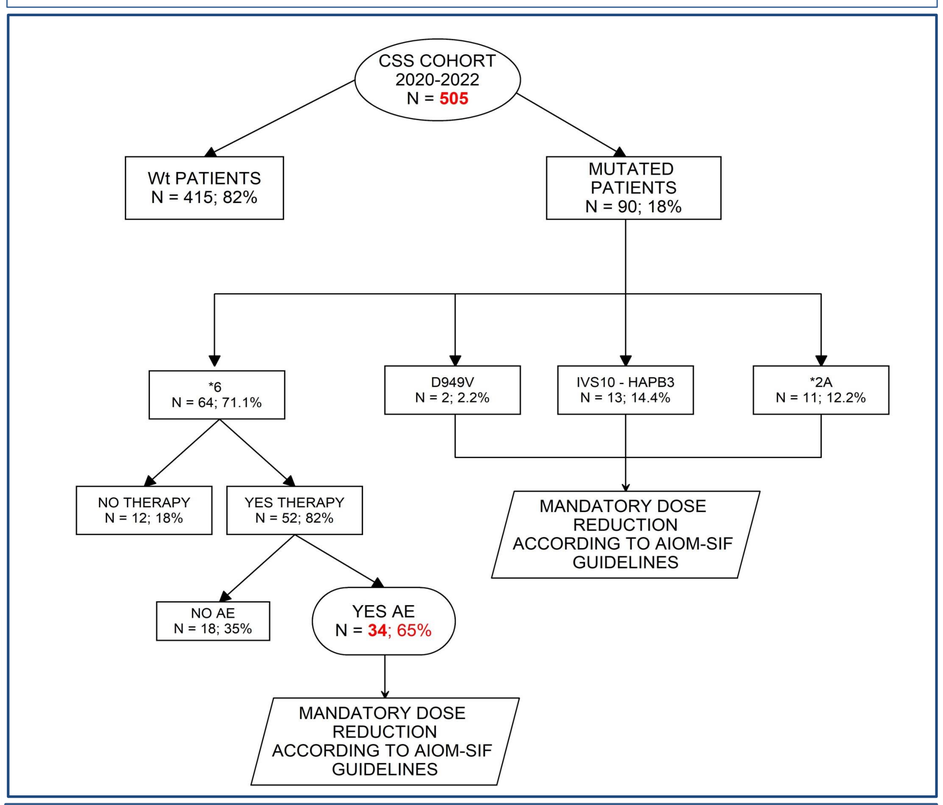


In the mutated patients subgroup, 44 out of 90 experienced FP-related toxicity. The most prevalent AEs are hematological (25/44 cases), primarily neutropenia, followed by gastrointestinal (13 cases), systemic, neurological, muco-cutaneous and cardiological.

We find that the *6 mutation is the most common mutation associated with AE hematological toxicities, particularly in grades 1 and 2.

MUTATION	TYPE OF TOXICITY					
N° of patients: 44/90	Hematologic n=25	Gastrointestinal n=13	Systemic n=11	Neurological n=7	Muco-Cutaneous n=4	Cardiological n=4
*6	17/44	12/44	10/44	6/44	3/44	3/44
*2A	4/44	0/44	0/44	1/44	0/44	0/44
IVS10	3/44	1/44	0/44	0/44	1/44	1/44
D949V	1/44	0/44	1/44	0/44	0/44	0/44

MUTATION AND HEMATOLOGICAL TOXICITY ONLY (25/44 PATIENTS)	
HEMA-AEs	TYPE OF TOXICITY
ANAEMIA	*2A (3/25); *6(2/25);
THROMBOCYTOPENIA	D949V (1/25); *6 (3/25)
NEUTROPENIA	*2A (1/25); *6 (9/25); IVS10 (1/25)
MULTIPLE HEMA-AEs	*6 (3/25); IVS10 (2/25)



CONCLUSIONS

Our analysis show that the *6 variant of the DPYD gene is the most common and is strongly associated with AEs, particularly neutropenia. In our study, 64 patients (12.6% of the total sample, 71% of the mutated subgroup) carry the *6 variant, with 34 of them experiencing AEs (65% of *6 patients undergoing therapy). As found in previous studies (1-2), it might be worth considering pre-emptive screening for the *6 variant before initiating FPs-based therapy, in addition to the other four mutations recommended by AIOM-SIF guidelines. These findings provide valuable information in the ongoing debate on the current strategy of dose reduction for *6 carriers, which is currently implemented only after the occurrence of AEs. Further research and evaluation are crucial in order to establish the validity and effectiveness of this approach.

REFERENCES

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