n°5PSQ-097

ATC:V03

TOXICITY ASSOCIATED WITH GENE POLYMORPHISMS IN PATIENTS WITH COLORECTAL CANCER, TREATED WITH FLUOROPYRIMIDINES AND ANALOGUES, IRINOTECAN AND PLATINUM COORDINATION COMPLEXES

G. LO CRICCHIO[1], G. SAIBENE[1], E. RUFFINO[1], G. LAGANÀ[1], C. DELLA COSTANZA[1], F. PIETRANTONIO[2], S. FALVELLA[3], F. NICHETTI[2], F.M. CELOTTI[4], V. LADISA[1].

[1]IRCCS ISTITUTO NAZIONALE DEI TUMORI FOUNDATION, HOSPITAL PHARMACY, MILANO, ITALY. [2]IRCCS ISTITUTO NAZIONALE DEI TUMORI FOUNDATION, MEDICAL ONCOLOGY, MILANO, ITALY. [3]UNIVERSITY HOSPITAL "LUIGI SACCO", BIOMEDICAL AND CLINICAL SCIENCES, MILANO, ITALY.[4]UNIVERSITY OF MILAN, PHARMACOLOGICAL AND BIOMOLECULAR SCIENCES, MILAN, ITALY.

Background

Gene variants, such as Single Nucleotide Polymorphisms, have a clinical relevance in oncological field, when they affect genes encoding enzymes involved in drugs metabolism, influencing drug toxicity, treatment compliance and efficacy.

Purpose

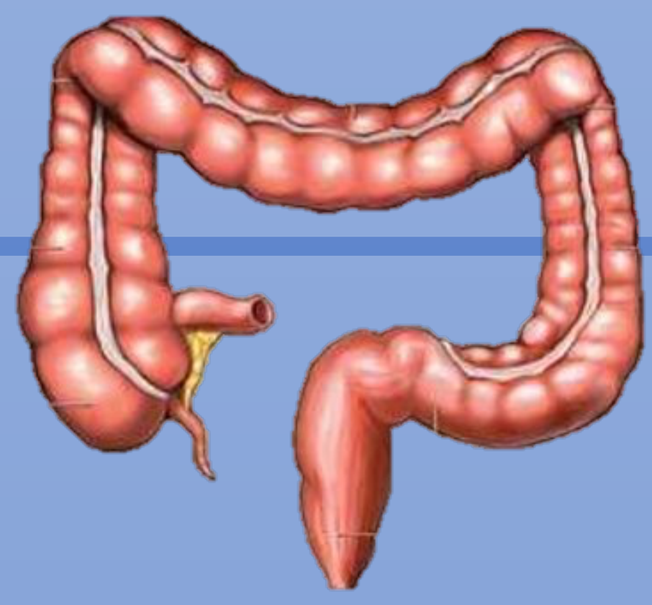
The purpose of this work is to obtain data to choose a personalized therapy based on individual gene variations, minimize adverse events (AE) and avoid the discontinuation of therapy resulting in tumor progression.

Material and methods

A retrospective study was conducted on 57 males and females, age ≥ 18, with colorectal cancer, in therapy with 5 protocols using different combinations of 5-fluorouracil, Irinotecan and Oxaliplatin.

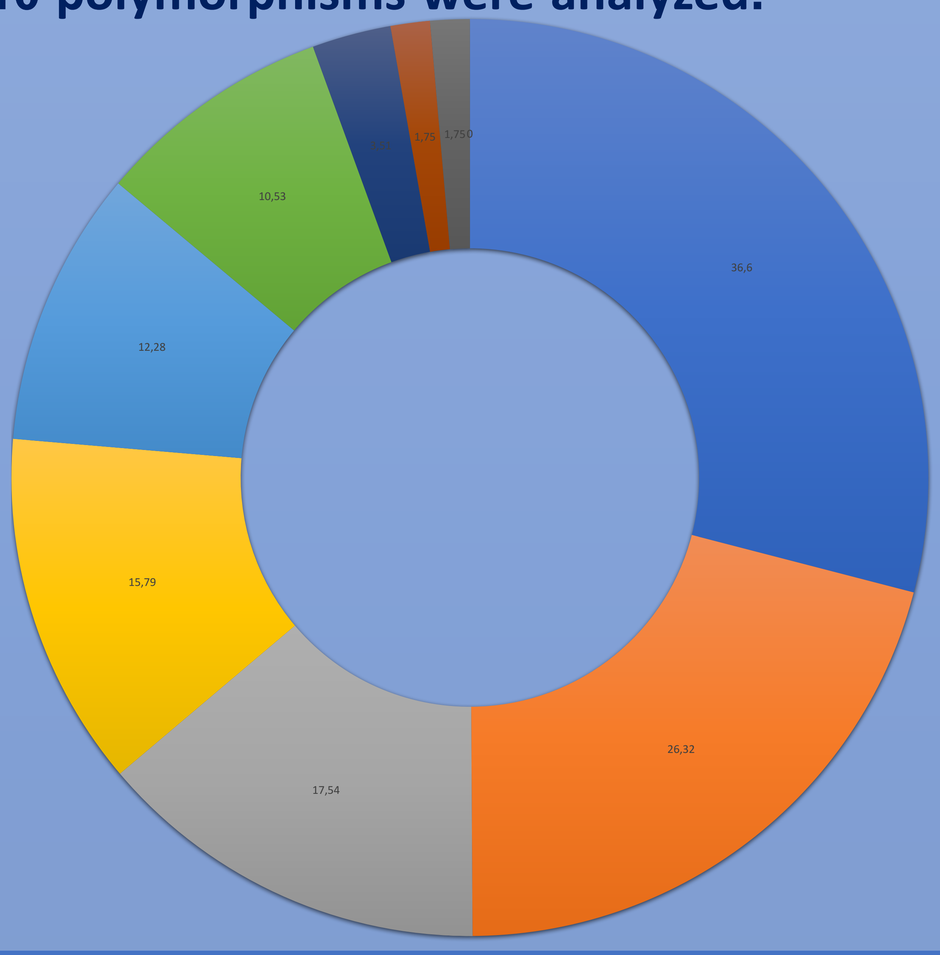
The study evaluated the number of cases where therapy was temporarily discontinued or suspended due to AE that concerned hematological, neurological and gastrointestinal toxicity according to CTCAE system, which provides a numerical grading scale for AE description.

The prevalence of polymorphisms and association between toxicity and polymorphisms were evaluated calculating ODDS Ratios (OR) with 95% confidence interval. Chi-square statistical significance test was applied.



Results

10 polymorphisms were analyzed:



OR values allowed finding the association between toxicity above 2nd grade and presence of polymorphisms. The association is:

- Strong positive for DPYD*2Ac.1905+1G>A (OR=10.68) and UGT1A1*28 (OR=7.43)
- Moderate positive for DPYDc.1129-5923C>G (OR=3.58) and SLC31A1 (OR=2.13)
- Moderate negative for ABCC2rs818 (OR=0.33)
- Absent for DPYD*13c.1679T>G, DPYDc496A>G, ABCC2rs717 and GSTPi

GENE	VARIANT	STANDARD GENOTYPE	TOXICITY >G2	OR (95% CI)	P VALUE
DPYD	*2Ac.1905+1G>A	GG	1,75%	10,68 (0,41-278,65)	NS
UGT1A1	*28	*1*1	22,22%	7,43 (0,81-67,83)	<5%
DPYD	c.1129-5923C>G	CC	1,75%	3,58 (0,21-61,62)	NS
SLC31A1	rs1098169 4T>G	TT	7,69%	2,13 (0,27-16,60)	NS
ABCC2	rs8187710(4544G>A)	GG	3,85%	0,33 (0,03-3,51)	NS
DPYD	*13c.1679T>G	TT	0%	1,07 (0,04-27,93)	NS
DPYD	c496A>G	AA	3,51%	0,96 (0,17-5,31)	NS
ABCC2	rs717620(-24C>T)	CC	3,85%	0,80 (0,07-8,91)	NS
GSTPi	rs1695(313°>G)	AA	11,54%	1,13 (0,15-8,21)	NS

Conclusion

Often patients express different polymorphisms at the same time, developing a toxicity related to the summed effects of all the polymorphic variants. This problem is particularly important for chemotherapeutics that are administered at very high doses, close to toxic doses, and takes on a clinical and economic relevance. The study of genes, involved in the metabolism and transport of many drugs, allows predicting drugs toxicity and efficacy and, based on individual variations, establishing a personalized and safe therapy before the beginning of the treatment.

23rd Congress of European Association of Hospital Pharmacists (EAHP), Gothenburg, Sweden, 21 to 23 March 2018