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Abstract Book

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Patients characteristics	N=20	%
Age, median (range)	54 years (26-68)	
Disease		
DLBCL	15	75
PMBCL	5	25
ECOG performas status at apheresis		
0	18	90
1	2	10
Stage at apheresis		
I-II	6	30
III	1	5
IV	13	65
Prior ASCT		
no	15	75
yes	5	25
CART type		
Tisagenleucel	15	75
Axicabtagene ciloleucel	5	25

T14

PERFECT CONCORDANCE BETWEEN BLOOD-BASED AND NORMAL TISSUE-BASED DIHYDROPYRIMIDINE DEHYDROGENASE (DPYD) POLYMORPHISMS SUGGESTS THAT PHARMACOGENETIC SCREENING COULD BE CONTEXTUAL TO TUMOUR MOLECULAR PROFILING

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Background: 5 – fluorouracil (5-FU) represents the chemotherapy backbone of almost all GI cancers. Important 5-FU-related toxicities have been traced back to impaired or reduced enzymatic catabolism secondary to DPYD allelic polymorphisms. International guidelines recommend pharmacogenetic DPYD test prior to treatment with fluorouracil, capecitabine, tegafur and flucytosine, and this usually requires an additional blood draw. The aim of our work was to evaluate the concordance of DPYD allelic variants detection from blood and normal tissue derived DNA in order to make the pharmacogenetic screening contextual to tumor mutation screening.
Patients and Methods: 5 standard DPYD gene polymorphisms (IVS14+1G>A, c.1905+1G>A; c.1679T>G, p I560S; c.2846A>T, p. D949V; c.1129–5923C>G, IVS10C>G; c.2194G>A, V732I) were tested both in blood-derived and normal formalin embedded tissue-derived cell DNA of consecutive GI cancers patients with Realtime Polymerase Chain Reaction (PCR) (Easy PGX ready DPYD – Diatech Pharmacogenetics). The adequacy of normal tissue availability on biopsy or surgical material had to be declared before testing by two dedicated pathologists (G.P and E.D.). Concordance of paired results was retrospectively evaluated.
Results: Nine Colorectal, 2 Esophago-Gastric Junction and 1 Pancreatic cancer patients were enrolled. Tissue samples were obtained from previous surgery or endoscopic biopsies. Pharmacogenetic evaluation was made before treatment start. Heterozygosis of rs1801160 polymorphism (c.2194G>A, V732I) was found in 4 out of 12 patients. Evaluation of heterozygous cases on paired blood and tissue samples showed a 100% overall agreement (Pearson's coefficient = 1). Concordance between blood and tissue-based results was also confirmed for the remaining 8 wild-type homozygous patients. As for international guidelines, 5 – FU administered dose was reduced by 15% in heterozygous patients. No grade > 1 fluoropyrimidine-related adverse events were reported in the whole cohort.
Conclusions: The fully concordant results in DPYD assessment between blood and tissue samples support the testing with Realtime PCR for genotyping of DPYD polymorphisms of GI patients on normal tissue when adequately available in routine clinical practice concomitantly with tumor genetic profiling (e.g. concomitant to RAS and BRAF mutation screening), thus avoiding the distress of an additional blood draw.

T15

RENAL FUNCTION IN CANCER PATIENTS UNDERGOING REPEATED ADMINISTRATIONS OF IODINATED CONTRAST MEDIUM (CM): A MULTICENTRIC RETROSPECTIVE STUDY

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Introduction: Contrast-enhanced computed tomography (CECT) is the imaging of choice for the diagnosis, staging, response evaluation, and follow-up of cancer patients; in fact, 47% of all CECTs are prescribed by Oncologists. Comorbidities, concomitant nephrotoxic (oncological and non-oncological) medications, as well as chronic dehydration from different causes, expose these patients to a higher risk of developing acute kidney injury (AKI) from CM. Risk factors, definition (PC-AKI vs CI-AKI), as well as preventive measures have been recently reconsidered, ultimately downsizing the incidence of this adverse event.

Materials and methods: The purpose of this study was to assess the effects of multiple and repeated CM administrations on the renal function in cancer patients on active treatment, collected from 5 Italian oncology departments. We have thus retrospectively evaluated 407 patients, who underwent at least 3 CECT (on the average 3.5) within one year (Table I).

Results: According to our study, neither significant differences in eGFR values, calculated with the CKD-EPI formula, between the baseline and the different post-CECT timepoints, nor AKI cases (defined according to the RIFLE criteria), were recorded.

Conclusions: Repeated and frequent CM administrations in cancer patients did not lead to a worsening of renal function, confirming that CI-AKI has a significantly lower incidence than previously thought; furthermore, 80% of the patients examined were found to be at low-risk. In concordance with the most recent guidelines, the administration of CM in oncological patients could be freely used, even in patients at higher risk.

Tab. I. Main characteristics of the population studied.

Age	>65	183 (45%)
	<65	224 (55%)
Sex	Male	228 (56%)
	Females	179 (44%)
Heart disease	Yes	79 (20%)
	No	274 (67%)
	Unknown	54 (13%)
Nephrectomy	Yes	171 (42%)
	No	236 (58%)
Diabetes	Yes	73 (18%)
	No	313 (77%)
	Unknown	21 (5%)
Hypertension	Yes	195 (48%)
	No	196 (48%)
	Unknown	16 (4%)
Kidney failure	Stages I and II	281 (69%)
	Stadio Iiia	85 (21%)
	Stadio Iiib	33 (8%)
	Stage IV	8 (2%)
	Stage V	0 (0%)
Type of tumor	Genitourinary	199 (49%)
	Gastro-intestinal	57 (14%)
	Lung	45 (11%)
	Head-neck	3 (0,8%)
	Cute	16 (4%)
	Udder	41(10%)
	Other	46 (11,2%)
Type of oncology therapy	Cytotoxic chemotherapy	175 (43%)
	Drugs with molecular target	134 (33%)
	Immunotherapy	142 (35%)
	Hormone therapy	16 (4%)

T16

PCSK9 INHIBITOR EVOLOCUMAB REDUCES CARDIOTOXICITY AND INFLAMMATION INDUCED BY DOXORUBICIN-TRASTUZUMAB THROUGH MYD88/NF-KB/MTORC1 PATHWAYS

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Introduction: Inhibition of proprotein convertase subtilisin/kexin type 9 (PCSK9) has emerged as a novel therapy to treat hypercholesterolaemia and related cardiovascular diseases. Evolocumab, a PCSK9 inhibitor, reduced the risk of cardiovascular events in patients with atherosclerotic cardiovascular diseases when added to maximally tolerated statin therapy (± ezetimibe), and recent data from the ODYSSEY OUTCOMES trial indicate that alirocumab added to maximally tolerated statin therapy (± other lipid-lowering drugs) reduces the risk of cardiovascular events in patients with a recent acute coronary syndrome. Considering the expression of PCSK9 in heart tissue, we aimed to study for the first time the direct biochemical effects of evolocumab in cardiomyocytes during exposure to doxorubicin, trastuzumab, their sequential treatments.

Methods: Human fetal cardiomyocytes (HFC cell line) were exposed to subclinical concentration of doxorubicin, trastuzumab, sequential treatment of both (all 100 nM), alone or in combination with evolocumab (50 nM) for 48h. After the incubation period, we performed the following tests: determination of cell viability, through analysis of mitochondrial dehydrogenase activity, study of lipid peroxidation (quantifying cellular Malondialdehyde and 4-hydroxynonenal), intracellular Ca2+ homeostasis. Moreover, pro-inflammatory studied were also performed (activation of NLRP3 inflammasome; expression of TLR4/MyD88; mTORC1 Fox01/3a; transcriptional activation of p65/NF-κB and secretion of cytokines involved in cardiotoxicity (Interleukins 1ß, 8, 6).

Results: Evolocumab co-incubated with doxorubicin alone or in sequence with trastuzumab exerts cardioprotective effects, enhancing cell viability of 35-43% compared to untreated cells ($p<0,05$ for all); Evolocumab reduced significantly the cardiotoxicity through MyD88/NF-KB/cytokines axis and mTORC1 Fox01/3α mediated mechanisms.

Conclusions: We demonstrated, for the first time, that the PCSK9 inhibitor evolocumab exerts direct effects in cardiomyocytes during doxorubicin and trastuzumab exposure turning on a new light on its possible use in cancer patients.