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GENOTYPING PANEL TO ASSESS HAND-FOOT SYNDROME IN T2DM AND CANCER PATIENTS WHO RECEIVE CONCURRENT PLATIN DERIVATES AND BIGUANIDES

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Abstract – *Objective:* *Different prevention strategies towards Type II Diabetes Mellitus (T2DM) patients with neuromuscular pain have been assessed in several studies. Recent data reported the correlation between genotype and neuromuscular events in patients, carrying both T2DM and cardiovascular disease, who were administered with statins-based therapy. In light of this, the present study was planned to evaluate whether Pharmacogenomics (PGx) profile can affect neuromuscolar pain in patients carrying T2DM and cancer. For this purpose, we have taken into account a panel of 4 polymorphisms on 4 candidate genes, already known as important markers related to Platin derivate and Biguanides (Pt-B) and peripheral neurotoxicity as "Hand-Foot syndrome" (HFS).*

Patients and Methods: *We genotyped 37 T2DM/cancer patients who underwent anti-diabetic and polypharmacy; 17 of them received concurrent platin derivates and biguanides therapy. Candidate variants were genes encoding drug transporters as ATP-binding cassette subfamily B member (ABCB1), subfamily C member 8 (ABCC8), and drug enzymes as Cytochrome P450 Family (CYP) including CYP2C8*3 and Glutathione S Transpherase P1 (GSTP1). An early evaluation of genotyping costs and benefits was also pointed out.*

Results: *Of 17 patients treated with Pt-B, 12 (65.7%) had adverse peripheral neuropathy events and 5 of them had HFS. Pharmacogenomics analysis showed a lack of any correlation between candidate genes polymorphisms and HFS toxicity. The genotyping results revealed that 14.1% of patients experienced grade >2 neurotoxicity, but none of them developed HFS (Odds Ratio [OR] 12.5, 95% CI 1.32-118.47,* p= *0.003).*

Conclusions: *The pharmacogenomic panel considered in the present work may play a decisive role in improving patients' treatments with both cancer and T2DM. Our experimental results support pharmacogenomics implementation, helping physicians in clinical decisions. Patients will be provided with a better treatment able to minimize neuromuscular pain and increase benefits, in term of both therapy efficacy and economy for national healthcare system.wellbeing.*

KEYWORDS: *Pharmacogenetics, Genotyping methods, Platin derivates, Biguanides, Neuromuscular pain.*

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INTRODUCTION

Several physicians acknowledge the importance of genetic variants in drug response and sustain the use of genetic test to plan tailored cure. Specifically, Pharmacogenomics and Pharmacogenetics (PGx) testing allow to stratify patients according to their drug response: those who can benefit most from treatments and those who experience adverse events at standard doses. Patients' stratification paves the way to the use of personalized treatments, reducing also delays in therapy administration[1]. For these evidences, PGx tests are an attractive option in Type II Diabetes Mellitus (T2DM) treatment of patients who receive polypharmacy due to cancer co-morbidities[2-4].

At present the therapy of choice in T2DM involves both a change in lifestyle and a drug therapy based on biguanides (i.e. metformin) and other oral antidiabetics drugs such as sulphonylureas Glinides (SU-G), thiazolidinediones (TZDs), glucagon-like peptide 1 (GLP-1) analogs, sodium-glucose cotransporter type 1 (SLTG1) inhibitors and insulines[5]. Drugs effect is strictly dependent on the functionality of both carriers involved in absorption and elimination of the drugs and Phase I enzymes as cytochrome P450 (CYP) family. For these reasons, the analysis of genetic variants involved in the abovementioned enzymes is crucial[6-8].

In our experience, during the clinical practice, we observed a singular peripheral hand and foot pain of T2DM in a subset of patients with cancer who receive concurrent therapies based on statins and Platin derivate and Biguanides (Pt-B). In order to investigate the probable genetic predisposition to HFS, we set out a genotyping panel to evaluate the genetic variants related to Pt-B[9,10] coadministration. From literature the Single Nucleotide Polymorphisms (SNPs) Glutathione S Transpherase P1 (GSTP1) Iso105Val were associated with hand and foot pain in patients treated with carboplatin, cisplatin and oxaliplatin[11].

Numerous efforts have been made to improve such drugs reaction (i.e. supplements with neuroprotective agents) without encouraging results[12,13]. Moreover, inter-individual variability in neuromuscular pain remains unsolved[14]. Although the association of several SNPs with the same adverse drug reactions has been reported in literature by different PGx studies, there are no studies outlining PGx and Pt-B coadministration. Furthermore, the knowledge of genes polymorphisms involved in transports and metabolism could be useful to predict neurotoxicity due to anti-diabetic treatment as shown in multiple studies and meta-analysis[15].

Based on our scientific hypothesis, we have verified a genotyping panel covering the abovementioned GSTP1 Iso105Val rs1695 and drug transporters ATP-binding cassette subfamily B member 1 (ABCB1, Alias MDR1), ATP-binding cassette subfamily C member 8 (ABCC8) and phase I enzymes of cytochrome P450 Family (CYP) including CYP2C8*3.

The evaluation of the described SNPs could contribute to prevent acquired and/or heritable adverse reactions in T2DM patients treated with Pt-B.

If the analysis of these SNPs will be routinely monitored into clinical practice, a further step towards personalized therapy will be taken. Nevertheless, the cost-effective ratio to support PGx tests is still controversial[16,17]. The aim of this pivotal work is to establish a validated genotyping panel for the prevention of HFS in T2DM patients undergoing Pt-B based therapy.

PATIENTS AND METHODS

Patient selection

The patients were recruited from the Institute for Study and the Cure of Diabetes (ISCD) "Abetaia" of Casagiove (CE), Italy. This retrospective work was performed in agreement with the Ethical values according to the Declaration of Helsinki. Informed consent documentation was reviewed and agreed by the independent Ethics Committee of ASL CE. In total, 37 diabetic patients (22 male and 15 female) were enrolled, 17 of whom received Pt-B based therapy (Table 1).

All patients had a diagnosis of diabetes and cancer (any type of carcinoma). They are currently treated with anti-glycaemic therapy and platin derivatives (only 17 cases in study cohort). The dose, schedule, and duration of diabetes therapy were not considered for genotyping.

The samples included 19 patients aged < 60 years (51.3%) and 18 aged ≥ 60 years, who were disjointedly analyzed in relation to risk factors for neuromuscular pain. Neuromuscular pain and HFS for any grade were also individually registered with a survey for all patients.

The inclusion criteria were patients with a diagnosis of T2DM with carcinoma co-morbidities. All enrolled patients presented no additional comorbidity such as Diabetic PolyNeuropathy (DPN).

Assessment of HFS was carried out using a survey based on symptom narration without consensus guidelines. In any single patient asymmetrical "stocking-glove" numbness, loss of deep tendon reflexes, and burning–tingling, were analyzed after therapy.

TABLE 1. Distribution variables of the case/control cohort: T2DM patients Pt-B users (n=17) vs. no Pt-B (Control cohort n=20). Univariate analysis.

	Patients			
	Control cohort n 20 (%)	*Pt-B users N 17 (%)*	*p-value**	*OR (95% CI)***
Age			0.06	
<60	8 (37.1)	11 (62.9)		1
≥60	12 (62.9)	6 (37.1)		0.41 (0.16-1.06)
Gender			0.04	
Male	9 (43.9)	13 (73.9)		1
Female	11 (56.1)	4 (26.1)		2.75 (1.04-7.29)
Medicines			nd	
Biguanides	20	17		
Thiazolidines	4	8		
GLP1 inhibitors	3	11		
Insulin	21	2		
Statines	19	15		
Platin derivates	20	17		
Adverse events			**0.001**	
No	14 (70.7)	5 (34.3)		1
Yes	6 (29.3)	12 (65.7)		4.7 (1.82-12.6)
DPN			**0.003**	
No	14 (70.7)	6 (34.5)		1
G1a & G1b	6 (29.3)	9 (51.4)		4.09 (1.49-11.18)
G2a & G2b	0 (0.0)	2 (14.1)		12.5 (1.32-118.47)
H&S Syndrome[§]			**0.02**	
No	18 (90.0)	12 (70.6)		1
Yes	2 (10.0)	5 (29.4)		4.35 (1.24-15.25)

*Chi-Square test; **Crude odds ratio logistic regression was adjusted for age and gender. [§]Not include DPN. It is based on individual anamnestic record. DPN: Diabetic Polyneuropathy.

Pharmacogenetic assay

Genomic DNA was extracted from a mouth swab in accordance with the manufacturer's protocol for the Ampli-DNA extraction kit (Dia-Chem srl, Naples, Italy).

The genotyping test was achieved using the TaqMan probe-based chemistry allelic discrimination assay in the OneStep platform (Life Technologies, Monza, Italy), following the manufacturer's protocols (Ampli-CYP, Ampli-MDR, and Ampli-GSTP-1, Dia-Chem srl, Naples, Italy). The panel test included the GSTP1, ABCB1, ABCC8, CYP2C8*3, polymorphisms.

Statistical Analysis

Differences according to age, gender, and adverse events, in particular for HFS, between Pt-B users and the control cohort were calculated using the Chi-square test Univariate analyses. The unadjusted logistic regression method was used to assess crude odds ratios (ORs) and 95% confidence intervals (CIs). Logistic regression models adjusted for age and gender were used to calculate adjusted ORs and 95% CI for each gene variants risk factors. All analyses were performed using SPSS for Windows, version 23.0 (IBM Corporation, Armonk, NY, USA). A two-sided *p*-value <0.05 was considered statistically significant.

RESULTS

Patients' reports

17 T2DM patients (4 female and 13 male) who received concurrent Pt-B therapy were included in the case-cohort. 12 of these (65.7%) experienced an adverse event, and 2 (14.1%) of them were grade 2a/b DPN (Table 1). 6 patients (17.1%) experienced peripheral neurotoxicity. The distribution of genetic variants correlated to risk factors is listed in Table 2. The control cohort consisted of 20 cases assuming concurrent therapy for cancer co-morbidity, without receiving Pt-B combination. Noteworthily, the case-cohort (12 Pt-B users) experienced more adverse events with respect to the 6 patients of control cohort: 65.7% and 28.6%,

TABLE 2. Distribution of genetic polymorphism according to risk factors (any grade HFS).

Gene Variants	*Patients Control cohort N= 20 (%)*	*Pt-B users N= 17 (%)*	*p-value**	*OR (95% CI)***	*SNP*	*Nucleotidic change*
ABCB1 Iso1145Iso			0.50		rs1045642	3435C>T
"CC"	8 (36.8)	6 (37.1)		1		
"CT"	11 (56.1)	9 (51.4)		0.57 (0.20-1.66)		
"TT"	1 (7.1)	2 (11.5)		1.67 (0.26-10.67).		
ABCC8 Arg1273Arg			0.40		rs1799859	-3C>T
"GG"	8 (36.6)	9 (54.3)		1		
"GA"	10 (53.4)	7 (39.6)		0.56 (0.21-1.47)		
"AA"	2 (10.0)	1 (6.1)		0.44 (0.07-2.76)		
GSTP1 Iso105Val			0.70		rs1695	342A>G
"AA"	12 (70.0)	11 (62.9)		1		
"AG"	8 (30.0)	6 (37.1)		1.25 (0.44-3.60)		
CYP2C8*3 Lys399Arg			0.19		rs10509681	1196A>G
"TT"	14 (75.7)	12 (71.4)		1		
"CT"	4 (16.2)	5 (28.6)		1.61 (0.49-5.36)		
"CC"	2 (8.1)	0		n.d.		

*Chi-Square test; **Crude odds ratio logistic regression was adjusted for age and gender.

respectively (p=0.001). In addition, Pt-B users experienced more diabetic polyneuropathy grade 2 than the control cohort patients (p=0.003). According to the individual anamnestic report, HFS was more significant in the case cohort than in the control cohort: 6 out of 17 patients (32.4%) and 2 out of 20 patients (10.0%) (p=0.02), respectively.

Genotyping assay

Fot the selection of the gene variants included in the pharmacogenomic panel, several criteria were considered: 1) searching polymorphisms known to influence the pharmacokinetics/pharmacodynamics of Pt-B (www.pharmgkb.org)[18]; 2) evaluating ongoing researches focusing on polymorphisms and adverse events and polypharmacy[15]; 3) considering issues concerning the cost-effectiveness ratio of PGx markers in clinical routine.

Table 2 summarizes the genotypes of all analyzed genes. The *ABCB1 3435C>T* rs1045642 (Iso1145Iso) genotype of Pt-B users was divided into two groups: TT allele (2 cases, 11.5%) *vs.* CT+CC alleles. The OR for every toxicity grade was 1.67 (CI: 0.26-10.67, p=0.50) for the minor allele when compared with CT+CC (medium and low risk, respectively) genotype.

The *ABCC8 -3C>T* rs1799859 (Arg1273Arg) genotype was divided into two groups: GG allele *vs.* GA +AA alleles (1 case, 6.1%). OR for every muscular pain grade was 0.44 (95% CI: 0.07–2.76, p= 0.40) for the wild type when compared with GA+ GG (medium and low risk, respectively) genotype.

GSTP1 342A>G rs1695 (Iso105Val) were divided into two groups: GG allele *vs.* AG genotypes. OR for any grade neuromuscular was 1.25 (95% CI: 0.44–3.60, p= 0.70).

*CYP2C8*3 1196A>G* rs10509681 (Lys399Arg) genotype was divided into two groups: TT alleles (12 cases, 71.4%) *vs.* CT alleles (5 cases, 28.6%). OR for every neuromuscular grade was 1.61 (95% CI: 0.49–5.35, p= 0.19) for CT (medium risk) genotype respect to TT genotype.

DISCUSSION

The use of PGx could be a useful predictive tool at disposal of clinicians, in order to optimize therapies. Nonetheless, there are some clear barriers concerning the ordinary clinical relevance of the selected SNPs panel analysis in anti-T2DM therapy: (i) the limited use of genotyping into daily clinical practice; (ii) the outstanding debates on PGx clinical utility and (iii) the cost-effectiveness[19]. Prospectively our study aims to assess a PGx panel for the prevention of HFS. We validated a cheap genotyping test using the TaqMan "allelic discrimination platform", which includes the detection of *ABCB1* (alias MDR1), ABCC8, GSTP1, and CYP2C8*3. From the analysis, no correlation between genotype and HFS adverse events was found.

The gene CYP2C8 encodes for an enzyme involved in phase I metabolism of Repaglinide. In subjects carrying linkage disaequilibrium (LD) dyplotype CYP2C8*3 rs11572080 (Arg139Lys) and rs10509681 (Lys399Arg) called ultrarapid metabolizer (UM), the drug is quickly eliminated[20-22]. Oth-

erwise, literature data reported that a small group of T2DM patients treated with SU (glimepiride, gliclazide, or glipizide) and carrying CYP2C8*3 experienced hypoglycemic events. As shown by our data, no statistically significant correlation was found between HFS (0 case) and CYP2C8*3 CC genotype (OR: 1.61, 95% CI: 0.49–5.36, $p = 0.19$), compared to the CT (medium-risk) genotype.

Genome-wide association studies (GWASs) focused on ABC transport proteins[23]SNPs concerning Platin derivatives toxicity highlighted two *ABCB1* SNPs (rs1045642, and rs2032586)[24] and *ABCC8* gene as possible candidate genes for genotyping.

SUR1 protein encoded by ABCC8 gene is part of K-ATP channel together with KIR6.2 protein encoded by potassium voltage-gated channel subfamily J member 11 (KCNJ11 gene). Different SNPs within the *ABCC8* locus influencing SUR1 protein have been related with interindividual variability in response to Pt-B treatment. The intronic polymorphism rs1799854 (exon 16 −3C → −3 T) is in LD with the variant rs1801261 (Thr759Thr). In nondiabetic relatives of T2DM patients, those polymorphisms seem to reduce insulin secretion after tolbutamide infusion[25]. Comparing T2DM patients carrying the rs1799854 CC *vs*.TT genotype treated with SU-G, there is a positive trend for the CC genotype in reducing HbA1c levels and enhancing insulin sensitivity as determined by HOMA index [26]. With regards to the synonymous SNP *ABCC8* rs1799859 (Arg1273Arg), most studies described that T2DM patients under SU-G treatment with the GG genotype had a significant increment in HbA1c levels compared with patients carrying the AA genotype[26]. Moreover, there is divergent opinion about the possibility that *ABCC8* rs1799854 Ala1369Ser is capable to interfere with SU-G therapy. In fact, a LD combines this SNP with the non-synonymous variant Lys23Glu in *KCNJ11.* Altogether, this leads to the consideration that for the herein examined genetic variant, at K-ATP channels, there is a molecular discriminatory specificity. Subjects with the 1369Ala and 23Lys haplotype, differently from the *ABCC8-KCNJ11* wild-type, were shown to develop an enhanced sensitivity to gliclazide[27]. Both polymorphisms rs1799854 and rs1799859 of *ABCC8* gene resulted remarkably correlated to increased level of triglycerides after hypoglycemic therapy[28].

CONCLUSIONS

The pharmacogenomic panel discussed in the present work will play a decisive role in improving controversial decisions concerning patients' treatment. We hypothesized that higher HFS pain in T2DM patients is not correlated to hypoglycemic therapy, but to Platin derivatives alone.

There have been several limitations in our research: i) lack of studies that include more cases to verify our preliminary data. The small number of subjects taken into consideration can lead to statistical inaccurancies[28]; ii) limited ethnicity to Caucasian population; iii) lack of criteria defining the toxicity grade of neuromuscular pain; iv) small samples size; v) The herein gene variants investigated were selected on the bases of recent GWAS findings, limited to significant correlations between PGx profile and SU-G/statin therapy. Further studies, concerning the considered gene variants, are needed to establish the utility and their possible application in clinical practice, with a benefit especially for the so-called "frail patients"[29].

Prospectively, with consistent results, we expect PGx test to enter into clinical routine for Pt-B treated patients. A clear advantage of PGx analyses is that they are cheap (about 50,00€/patients) and accessible for laboratories equipped with Real time-PCR strumentation[30].

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Ethical Declaration:
This retrospective work was performed in agreement with the Ethical values according to the Declaration of Helsinki.

Informed consent:
Informed consent documentation was reviewed and agreed by the independent Ethics Committee of ASL CE.

Conflict of interest:
MPO and GM, are employed by DIACHEM srl, Viale Privato Rai, 7. Napoli. Other authors declare no conflict of interest.

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