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VALIDATION OF A SIMPLE GENOTYPING PANEL ASSAY FOR PHARMACOGENOMICS OF TAXANE-BASED THERAPY: PRELIMINARY RESULTS

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ABSTRACT – *Objective:* Several strategies for preventing toxicity and resistance to taxane-based chemotherapy have been investigated so far. Lately, findings on the genetic variants associated with neutropenia and neuropathy (N&N) toxicity have been reported.

Patients and Methods: A panel assay of single nucleotide polymorphisms (SNP) related to paclitaxel and Docetaxel toxicity on four candidate genes *ATP-binding cassette subfamily B member 1 (ABCB1), Beta-tubulin 2A (TUBB2A), Cytochrome P450 3A4* 1B (CYP3A4*1B), Excision-Repair Cross-Complementing group 2 (ERCC3)* are validated and discussed. We genotyped 37 cancer patients who received paclitaxel or docetaxel-based therapy. Furthermore, an early outline evaluation of the genotyping costs and benefits was assessed.

Results: A total of 37 patients were treated with a taxane of which 17 (45.9%) had adverse N&N events. Pharmacogenomics analysis showed no relation between candidate gene polymorphisms and toxicity, except for the ERCC3 AG+GG allele [OR 2.61 (95% CI: 0.91–7.61)] that showed a significantly weak trend of risk of neurotoxicities *vs.* the AG allele [OR 1.52 (95% CI: 0.51–4.91)] p=0.03.

Conclusions: We propose a useful genotyping panel assay to prevent toxicity in patients undergoing taxane-based therapy at an affordable price, with help from the literature and our experimental results and data. Based on the individual pharmacogenomics profile, clinicians will have additional information to personalize the treatment for the patient to minimize toxicity and maximize benefits, and they can also determine the cost-effectiveness for national healthcare sustainability.

KEYWORDS: Genotyping methods, Docetaxel, Paclitaxel, *ABCB1*, MDR1, Beta-tubulin 2A (TUBB2A), *CYP3A4*1B, ERCC2.*

INTRODUCTION

Toxicity to taxane-based therapy is well-documented and often leads to discontinuation of treatment. Adverse events are reported as neutropenia and neuropathy (N&N). Mainly acute peripheral neuropathy has been linked to acute and cumulative doses of taxane[1]. Mechanisms of neurotoxicity are related to microtubule disturbances in the dorsal root ganglia, axons, and Schwann cells. In particular, the protein Beta-tubulin 2A (TUBB2A) seems to have a genetic variant related to the assembling of the microtubule. Many efforts have been made in an attempt to develop strategies for reducing toxicities (e.g., using neuroprotective agents), although these attempts have yielded only modest achievements[2]. Moreover, to a large extent, inter-individual variability in neurotoxicity remains unexplained. In the last decade, numerous Pharmacogenomics (PGx) studies have reported several SNP associated with the same adverse drug response in cancer[3]. A recent clinical study has shown that neurotoxic events can be predicted through the identifications of SNP known to be involved with taxane transports, biotransformation, and DNA damage repair gene[4]. Recently, the well-known synonymous SNP ATP-binding cassette subfamily B member 1 (ABCB1 alias MDR1) 3435 C>T (rs1045642) showed a notably lower overall survival rate than the CC genotype for the allele variant, in patients with metastatic breast cancer[5]. Another study found greater clearance of docetaxel in patients with the Cytochrome P450 (CYP) 3A4*1B[6]. Other small studies have found lower clearance of paclitaxel related to the CYP2C8*3allotype[7]. The DNA repair protein Excision-Repair Cross-Complementing group 2 (ERCC2 alias XPD) Lys751Val is related to severe non-haematological toxicity[8]. Based on these scientific evidences, we have validated a genotyping panel assay containing the most relevant pharmacogenomic markers on 7 genes, including, *ABCB1 (Alias MDR1)*, *TUBB2A*, *CYP3A4*1B*, *CYP2C8*3*, and *ERCC3*. Additional SNPs on *Glutathione S-Transferase*1 *GSTP1* Ile105Val were also included. The goal of this experimental pilot work is to establish a validated genotyping panel assay for the prevention of neurotoxicity in patients for whom taxane-based therapy is planned. Oncologists will thus have a new tool aimed at both toxicity and/or adopting the optimal scheduling approach to minimize cumulative neurotoxicity in taxane-based therapy.

PATIENTS AND METHODS

Patient selection

The DNA samples from anonymous cancer patients were collected at the "Research lab CETAC" Caserta (CE), Italy. This retrospective work was performed in compliance with the ethical values laid down by the Declaration of Helsinki, and informed consent documentation was reviewed and agreed upon by the independent Ethics Committee. All patients signed the informed consent for genetic studies. The study was planned to measure whether the PGx profile can affect taxane-induced N&N. In total, 37 cancer patients who received adjuvant taxane-based chemotherapy were selected. All patients had a diagnosis of carcinoma (primarily, breast, ovarian, genitourinary, etc.) and were treated with paclitaxel- or docetaxel. The standard chemotherapy dosage schedule and duration were as follows: for paclitaxel 175 mg/m^2 intravenously (IV) every 3 weeks for 4 cycles, (for adjuvant treatment for breast cancer) and/or 80 mg/m^2 weekly IV for 12 cycles, and for docetaxel IV 100 mg/m^2 for 4 cycles for first line metastatic cancer. The samples were separated into two arms: those with (17 control) and those without (20 cases) N&N grade ≥2 toxicity.

Pharmacogenomic panel assay

Genomic DNA was extracted with a mouth swab following the manufacturer's protocol using an Ampli-DNA extraction kit (Dia-Chem, srl, Naples, Italy). The genotyping assay was performed using the TaqMan probe-based chemistry allelic discrimination assay in the OneStep platform (Life Technologies, Monza, Italy). The investigating panel test included the ABCB1 (alias MDR1), TUBB2A CYP3A4*1B, GSTP1, and ERCC2, polymorphisms. The reaction mix and temperature protocol (95°C for 15 and 60°C for 1 min for 40 cycles) were performed in accordance with the manufacturer's protocol (Ampli-taxan, Dia-Chem, Naples, Italy).

Statistical analysis

Differences according to therapy, and adverse events, in particular, who report N&N adverse events in the whole cohort of taxane users were calculated using the Chi-square test. Univariate analyses were performed to match the two arms: the unadjusted logistic regression method was used to assess crude odds ratios (ORs) and 95% confidence intervals (CIs). Logistic regression models adjusted for major confounders like age and gender were used to calculate adjusted ORs and 95% CIs for each gene variant's risk factors. Analyses were carried on using SPSS for Windows, version 23.0 (IBM Corporation, Armonk, NY, USA). A bilateral $p < 0.05$ was considered statistically relevant.

RESULTS

Samples reports

Thirty-seven DNA samples from cancer patients who received adjuvant taxane-based therapy were analyzed in this retrospective study. Of these, 17 (45.9%), had experienced an adverse event of > grade 2 N&N toxicity (Table 1).

Table 1. Selected case/control samples Taxane users (cohort *n* = 37): Univariate analysis.

	Taxane users samples		*p*-value*	OR (95% CI)**
	***Case* cohort *n20* (%)**	**Control *n17* (%)**		
Age			0.06	
< 60	8 (41.5)	11 (62.9)		1
≥ 60	12 (58.5)	6 (37.1)		0.42 (0.16–1.06)
Gender			0.04	
Male	9 (48.8)	4 (25.7)		1
Female	11 (51.2)	13 (74.3)		2.75 (1.04–7.29)
Type of cancer			nd	
Breast	12	7		
Gastric	1	2		
Other	7	8		
Adverse events			**0.001**	
No	14 (70.7)	6 (34.3)		1
Yes	6 (29.3)	11 (65.7)		4.7 (1.82–12.6)
Neutro & Neuro			**0.003**	
No	14 (70.7)	6 (34.3)		1
G1 & G2	5 (26.8)	9 (51.4)		4.09 (1.49–11.18)
G3 & G4	1 (2.4)	2 (14.3)		12.5 (1.32–118.47)
Neutropenia			**0.02**	
No	17 (90.2)	12 (68.6)		1
Yes	3 (9.8)	5 (31.4)		4.35 (1.24–15.25)
Neuropathy			0.3	
No	18 (90.2)	14 (82.9)		1
Yes	2 (9.8)	3 (17.1)		1.96 (0.51–7.62)

*Chi-Square test;

***Crude odds ratio logistic regression was adjusted for age and gender. Significative results are in bold.*

Genotyping profile

To set up pharmacogenomic panel tests, several criteria were considered for selecting gene variants: (i) search on the whole standardized polymorphisms acknowledged to have an impact on. The pharmacokinetics/pharmacodynamics of taxanes (www.pharmgkb.org); (ii) review of current researches, particularly trials including polymorphisms related to toxicity; (iii) identification of issues related to the impact of genotyping testing which might provide answers concerning the incorporation of PGx markers in clinical practice.

The ABCB1 3435C>T rs1045642 Iso1145Iso allotype of taxane users was divided into two groups: TT allele *vs.* CT+CC alleles (2 cases, 11.5%). The OR for every toxicity grade was 1.67 (0.26–10.67, p= 0.05), when compared with CT+CC (medium and low risk, respectively) allele genotype.

The ABCB1 2677G>T/A rs2032582 Ala893Ser genotype was divided into two groups: TT/AA allele *vs.* GT/A and GG alleles (1 case, 6.10%). OR for every toxicity grade was 0.44 (95% CI: 0.07–2.76, p=0.40), when compared with GT/A+ GG alleles (medium and low risk, respectively) allele genotype.

The CYP3A4^{*1B}–392A>G rs2740574 5'UTR genotype was divided into two groups: AG+GG risk allele *vs.* AA alleles (4 cases, 25.7%). OR for every toxicity grade was 0.60 (95% CI: 0.20–1.83, p = 0.70), when compared with AA (low risk) allele genotype.

B-Tubulin IIa -101C>T/- 112G>A rs909964/rs909965 (linkage disequilibrium) 5'UTR genotype was divided into two groups: CT allele *vs.* TT alleles (5 cases, 28.6%). The OR for every neuropathy grade was 1.62 (95% CI: 0.49–5.35, *p*= 0.19), when compared with CT (medium risk) allele genotype.

The *GSTP1* Iso105Val rs1695 genotype was divided into two groups: GG allele *vs.* AG+AA genotypes. The OR for any grade neuropathy was 1.25 (95% CI: 0.44–3.60, p= 0.71).

The *ERCC2 2251T>G* Lys751Gln rs13181 genotype was divided into two groups: AA *vs.* GA and GG genotypes. The OR for any neuropathy grading was 1.52 (95% CI: 0.51–4.91) for GA alleles, and the OR for GG+GA was 2.61 (95% CI: 0.91–7.61); p= 0.031.

Genotyping costs

Multiple genotyping methods have been validated for assessing the genetic profile of the aforementioned SNPs, but no gold standard has been defined. Moreover, only a few studies have addressed the cost-effectiveness of pharmacogenomic testing in terms of the implications for clinical practice[9]. For instance, an early outline of the genotyping costs for "home-made tests" using allele discrimination on the fluorescent-based platform, was calculated at about €20,00 per SNP[10]. The realistic selection of our Pharmacogenomic panel assay interrogates 5 polymorphisms, and its cost is averaged to €100,00.

DISCUSSION

The aim of our study is to propose a validated PGx panel assay for the prevention of N&N in patients who planned taxane-based therapy. We developed an inexpensive panel test using the TaqMan "allelic discrimination platform" including the homogeneous detection of five polymorphisms on four genes: ABCB1 (alias MDR1), TUBB2A, CYP3A4$^{*1B,\ GSTP1}$, and ERCC2. As shown previously, polymorphisms in ABCB1 and CYP3A4^{*1B}, are able to predict taxane neurotoxicity[5]. Our results for ABCB1 (alias MDR1) ABCB1 3435C>T allele TT and CYP3A4$^{*1B\ 392A}$>G AG+GG don't confirm the previously published data due to low cohort of taxane users[5]. Here, we evaluated additional SNPs on the candidate genes: TUBB2A, GSTP1 and ERCC2, but did not observe a significant relationship with N&N except for ERCC2 2251T>G Lys751Gln rs13181 for GG+AG alleles (p = 0.03). Despite the low correlation with taxane toxicity (see Results), we believe that any of these polymorphisms could play a key role in the acquired cellular resistance due to DNA repair genes (ERCC2); this is why they were included in the proposed genotyping panel assay (Table 2).

For *ABCB1*, two SNPs (rs1045642 and rs2032586) have been related to the upper serum level of docetaxel, and grade 2–3 neurological toxicity compared to patients with other genotypes. Grade ≥2 neurotoxicity has been found to be highly recurrent in patients with the *ABCB1 3435TT* allotype in comparison to the CC/TC (OR: 2.76, 95% CI: 1.17–6.49, *p* = 0.017)[5]. The same study showed that the *CYP3A4*1B 392AA* and AG alleles are predictive of only grade >1 neuropathy, (OR 2.26, 95% CI: 1.03–4.94, *p* = 0.038)[5].

Table 2. Results of genotyping in according to toxicity (neutropenia and neuropathy).

Gene variants	Cases 37 (all treated with taxane)		*p*-value*	OR (95% CI)**
	Case No Resis/ Tox *N* = 20 (%)	Control Resist/ Tox *N* = 17 (%		
ABCB1 Iso1145Iso			0.050	
"CC"	7 (36.6)	6 (37.1)		1
"CT"	11 (56.1)	9 (51.4)		0.57 (0.20–1.66)
"TT"	2 (7.3)	2 (11.5)		1.67 (0.26–10.67)
ABCB1 Ala893Ser			0.400	
"GG"	7 (36.6)	8 (54.3)		1
"GT/A"	11 (53.7)	7 (39.6)		0.56 (0.21–1.47)
"TT/AA"	2 (9.8)	1 (6.1)		0.44 (0.07–2.76)
CYP3A4*1B 5'UTR			0.040	
"AA"	14 (70.7)	13 (74.3)		1
"AG+GG"	6 (29.3)	4 (25.7)		0.60 (0.20–1.83)
B-Tubulin IIa -101C>T/-112G>A			0.19	
"TT"	15 (75.7)	12 (71.4)		1
"CT"	3(16.2)	5 (28.6)		1.62 (0.49–5.35)
"CC"	2 (8.1)	0		n.d.
GSTP1 Iso105Val			0.70	
"AA"	12 (70.0)	11 (62.9)		1
"AG"	8 (30.0)	6 (37.1)		1.25 (0.44–3.60)
ERCC2 Lys751Gln			0.031	
"AA"	17(82.9)	11 (65.7)		1
"AG"	3(17.1)	4(20.0)		1.52 (0.5–4.91)
"GG"	0	2 (14.3)		n.d.
"AG"+"GG"		6 (34.3)		2.61 (0.90–7.61)

Several observational PGx types of research using genome-wide association studies (GWASs) have focused on SNPs related to taxane neurotoxicity, but the results have still been inconclusive and are not sufficiently clinically relevant. The polymorphism *CYP2C8*3* gene (rs10509681) has been found to be related to a decrease in the metabolic activity of paclitaxel and associated with potential increases in neuropathy risk[11]. A further study found that breast cancer patients with the *CYP2C8*3* allele achieved further clinically relevant outcomes using adjuvant paclitaxel (55 *vs.* 23%; OR: 3.92, 95% CI: 1.46–10.48, corrected $p = 0.046$) but a higher frequency of >grade 2 neurotoxicity was recorded (22 *vs.* 8%; OR: 3.13, 95% CI: 0.89–11.01, $p = 0.075$). No difference was found in either European-American or African American patient cohorts[12]. So far, many studies have found *CYP2C8*3* to be statistically significant, but many others have failed to do so[13]. Di Francia *et al*[13] discovered a statistically insignificant relationship between neurotoxicity (6 cases) and polymorphism for the *CYP2C8 CC* genotype (OR: 1.62, 95% CI: 0.49–5.35, $p = 0.19$), compared to the CT (medium-risk) genotype.

Another study of 239 patients receiving paclitaxel, performed the *CYP2C8*3, CYP2C8*4, CYP3A4*22*, and *ABCB1 3435 C>T* genotypes. *CYP3A4*22* carriers were correlated with an increased risk of severe neuropathy ($p = 0.043$). In addition, this study showed that poor metabolizers (PMs) for *CYP3A4*22 GG* polymorphism were related to the severe neurotoxicity of paclitaxel compared to the TT and CT genotypes[14]. In our study, the OR was 2.17 (95% CI: 0.48–9.79, $p = 0.30$), in favor of the CT genotype.

In addition, the *GSTP1* Ile105Val polymorphism *313A>G* (alias *GSTP1*B*), was related to low enzyme "Glutathione detox" capacity[15]. As previously demonstrated, in patients with adeno-colorectal cancer treated with a 5-FU and oxaliplatin schedule, the GSTP1 Ile105Val heterozygous status was related to an augmented risk of neuropathy, while patients with Val/Val status had a lower neurotoxicity risk profile and tumour aggressiveness than Ile/Ile phenotypes[16]. To date, no evidence has been reported for taxane neurotoxicity. This GSTP1313A>G variant may be identified by a simple and cheap allelic discrimination method[17]. Given such evidence, we genotyped the taxane users and control cohort but found no statistically relevant correlations.

It is known that the DNA repair system is a principal mechanism for direct (i.e. platinum agent) and indirect (i.e., docetaxel) resistance to chemotherapy. Since the cell is capable of restoring the damaged DNA, the apoptosis induced by chemotherapeutic agents fails. The nucleotide excision DNA repair cross-complementation group 2 *ERCC2* non-synonymous Lys751Gln SNP *2251A>C* (rs13181) has still not been recognized as taking part in the mechanism of taxane toxicity/resistance. Our data confirm the lack of correlation as previously described by other authors[5].

It has been reported in a meta-analysis that *XRCC3 316A>G* Thr241Met (rs1799794), a DNA repair protein, is related to response to platinating agents, which highlights the prognostic value of *XRCC3* Thr241Met polymorphism in patients with lung cancer. A meta-analysis of a total of 14 appropriate studies including a total of 2828 patients treated with platinum drugs showed that subjects with the variant 241Met phenotype resulted statistically significant (good outcome) in comparison to those carrying the wild-type 241Thr phenotype (Met *vs.* Thr, OR = 1.453, 95% CI: 1.116–1.892, p = 0.968 and Thr/Met+Met/Met *vs.* Thr/Thr, OR = 1.476, 95% CI: 1.087–2.004, p = 0.696). This noteworthy connection was identified in the Caucasian but not in the Asian population[8]. The functional effect of these variants on taxane molecules is low. It has been reported *XRCC3 316GG+GA* alleles yielded statistically significant for all neutropenia grades was 2.61 (95% CI: 0.91–7.61) p = 0.03[13]. To date, these results are not confirmed by others and no study on clinical trials has been published. Additional gene variants influencing the pharmacodynamics of taxane have been documented. They included Beta-tubulin 2A (TUBB2A) and the role of the polymorphisms rs909964 and rs909965 detected by GWAS. These variants need more evidence in confirmatory studies. In addition, it was associated with pharmacokinetic outcomes but not in neuropathy/neurotoxicity.The clinical effectiveness of the polymorphism described here could help in developing new diagnostic tools for driving treatment decisions[17]. In particular, molecular testing for a mutation in the ABCB1 (alias MDR1), CYP3A4$^{*1B,\ CYP2C8*3}$, and ERCC2 genes will possibly help oncologists to select subjects who are most expected to avoid taxane neurotoxicity. For assessing a basic profile of patients responding well/poorly, a panel test of five genetic variants is planned (Table 2). The aspects addressed here could help clinicians to stratify patients' profiles from genotype A (the most likely responders to treatment) to genotype C (bad responders with higher odds risk of acute and cumulative neurotoxicity). The PGx profile defined as low risk for toxicity showed wild-type expression of ABCB1 (3435CC and 2677GG), conferring the normal intrusion/extrusion of taxane and active metabolites. In addition, the regular CYP2C8 and CYP3A4 392GG allotypes ensure appropriate metabolic activity. Pharmacogenomic profiles can show a predisposition to a higher neutropenia and neuropathy risk by revelling higher transmembrane expression of the ABCB1 (3435TT and 2677TT/AA), variant phenotype, conferring the excessive extrusion of taxane from neoplastic cells wich causes high plasma concentration. Also, poor metabolic activity due to CYP3A4^{*1B} (392 AA/AG) causes pharmacokinetic problems, and lower expression of the ERCC3 316AG/GG phenotype probably meddles with DNA replication of neoplastic cells and is less likely with that of hematopoietic cells, resulting in severe neutropenia, as previously observed in a Caucasian population[8]. There have been certain restrictions in our projected panel tests: (i) these PGx signatures need to be validated in multiple clinical trials with a larger number of patients; (ii) our genotyping data are limited to a Caucasian population; (iii) we did not adjust our data for multiple comparisons (i.e., type of cancer) due to a low number of cohort samples; (iv) the selection of the gene variants was made on the basis of recent findings in clinical trials with significant interconnection between the PGx profile and taxane treatments. However, with regard to the gene variants analyzed in this pilot study, the single endpoint was to evaluate the usefulness and cost-effectiveness of a PGx panel assay right for application in clinical practice, with particular attention to so-called "frail patients" who receive polytherapy due to comorbidity[18].

Furthermore, defining an individual PGx profile does not afford a unique target to assess the optimal strategic approach for the management of taxane-induced neuropathy; thus, it is necessary to seek complementary and alternative medicines[19], as well as to look at nutrition[20].

In the next few years, it can be expected that there will be links between pharmaceutical and biotechnology companies to undertake larger and broader studies validating tests available for routine diagnostics in pharmacogenomics concerning paclitaxel and docetaxel[21]. Currently, our proposed pharmacogenomic panel assay is useful because it is low cost (about €100,00/genotype/patient) and it is suitable for most clinical laboratory with real time-PCR equipment. In addition, high genomic expertise is not needed to interpret genotype results (Table 2).

If the detection and predictive value of these SNPs on aforementioned genes are regularly incorporated into clinical procedures, the personalized therapy should be scheduled[22].

CONCLUSIONS

In summary, clinicians and laboratory managers should join in evaluating the benefits and limitations, particularly regarding costs and applicability, of the pharmacogenomic tests that are likely suitable for a routine clinical practice integration.

Ethical approval and consent to participation:

Informed consent documentation was reviewed and agreed upon by the independent ethics committee. All patients signed consent for participation to research study as anonymous.

Consent for publication:

All authors signed consent for publication and copyright agreement. All patients signed consent for data publication as anonymous.

Availability of data and material:

No additional data reported.

Conflict of interest:

The authors declare that researches were conducted in absence of any kind of commercial and financial relationships that could be considered as conflict of interest.

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Author contributions:

RDF and AV study designed and wrote the draft. MDP, SP, and EV recruited patients and samples. LDF analyzed the samples. CD, MM and LA data and results elaboration. VDL and AV analyzed statistically the results. RDF expert supervision and correction of the manuscript.

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