

ORIGINAL PAPER

TAXANE TREATMENT OUTCOMES IN HISTOLOGICALLY CHARACTERIZED ALGERIAN LUNG CANCER PATIENTS: A POPULATION-SPECIFIC EXPLORATORY STUDY OF *CYP3A4*, *CYP2C8*, AND *ABCG2* VARIANTS

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Introduction: Taxane-based chemotherapy remains a cornerstone of lung cancer treatment, but its clinical use is often limited by dose-dependent toxicities, particularly peripheral neuropathy. In this retrospective study of 110 Algerian patients with lung cancer, we evaluated the influence of germline polymorphisms, distinct from tumor somatic alterations, on treatment outcomes, while considering World Health Organization classified histological subtypes.

Material and methods: Based on their roles in taxane metabolism and transport, *CYP2C8*, *CYP3A4*, and *ABCG2* were selected for analysis. Germline polymorphisms *CYP2C8* c.416G>A, *CYP3A4* g.392A>G, and *ABCG2* c.421C>A were genotyped using TaqMan PCR, and their associations with treatment response, adverse events, and dose modifications were analyzed using SPSS, Epi Info 7, and R-Studio.

Results: The results showed that the *CYP2C8* c.416G>A polymorphism was not significantly associated with chemotherapy response or neuropathy incidence. The *ABCG2* c.421C>A polymorphism was not significantly associated with treatment efficacy or peripheral neuropathy, but it was related to cumulative taxane exposure. The *CYP3A4* g.392A>G polymorphism was associated with increased peripheral neuropathy severity. Adenocarcinoma histology was also significantly associated with treatment response ($p = 0.01$), underscoring the value of integrating histopathological and pharmacogenetic factors.

Conclusions: These population-specific findings support further investigation of pharmacogenetic stratification in larger lung cancer cohorts.

Key words: lung cancer, pharmacotoxicity, genetic polymorphisms, cytochromes P450, *ABCG2* transporter, personalized medicine.

Introduction

Lung cancer represents the leading cause of cancer-related mortality worldwide, with non-small cell lung

cancer (NSCLC) accounting for approximately 85% of all cases [1]. Accurate histological classification is fundamental to lung cancer management, as diagnostic and therapeutic decisions increasingly rely

on distinguishing major subtypes, particularly adenocarcinoma and squamous cell carcinoma, along with their molecular characteristics and therapeutic implications [2, 3]. In advanced stages of the disease, treatment response is influenced by both tumor-specific factors (e.g., molecular alterations, immune microenvironment) and host-specific factors, including individual pharmacogenetic profiles.

Contemporary pathology practice has evolved toward integrated diagnostic approaches that combine morphological assessment with comprehensive molecular profiling. Pathologists now work within multidisciplinary teams, using next-generation sequencing, immunohistochemistry, and liquid biopsy techniques to identify actionable mutations in key genes including epidermal growth factor receptor “EGFR”, anaplastic lymphoma kinase “ALK”, *proto-oncogene tyrosine-protein kinase “ROS1”* [4, 5]. This integrated approach enables personalized treatment selection, especially in advanced NSCLC where histology-specific therapies such as pemetrexed for non-squamous histology or bevacizumab contraindications in squamous cell carcinoma have demonstrated differential efficacy [6–8].

In precision oncology, both the somatic tumor genome and the patient’s germline genome contribute to treatment individualization. While somatic alterations primarily inform tumor biology and therapeutic sensitivity, germline pharmacogenetic variants in drug-metabolizing enzymes and transporters modulate drug exposure, toxicity, and administration [9, 10]. This distinction is clinically relevant: tumor molecular profiling guides targeted therapy selection, whereas germline pharmacogenetic testing can predict adverse drug reactions and optimize dosing strategies.

Paclitaxel and docetaxel are established taxanes that have long remain central to platinum-based chemotherapy for advanced NSCLC. As microtubule-stabilizing agents, they disrupt mitotic progression and promote apoptosis, but their clinical use is hampered by marked interindividual variability in pharmacokinetics and toxicity [11, 12]. Peripheral neuropathy a major dose-limiting toxicity, affects 60–70% of patients receiving paclitaxel and frequently necessitate dose reduction or treatment discontinuation [13].

The pharmacokinetic disposition of paclitaxel is significantly modulated by cytochrome P450 enzymes and drug transporters. Its biotransformation is primarily mediated by Cytochrome P450 Family 2 Subfamily C Member 8 (CYP2C8) and Cytochrome P450 Family 3 Subfamily A Member 4 (CYP3A4), which catalyze its oxidative clearance into inactive metabolites such as 6 α -hydroxypaclitaxel and 3’-p-hydroxypaclitaxel [14, 15]. These metabolites are subsequently eliminated *via* biliary and urinary excretion [11]. Particularly, paclitaxel is a substrate of the efflux transporter ABCG2 (BCRP), expressed in the intestine, liver, and kidney, which contributes to transmembrane drug transport and elimina-

tion [16]. Genetic variations in these pathways can alter drug clearance and exacerbate toxicity risk [17].

The CYP3A4 gene (7q21.1–q22.1) (27 kb, 13 exons) encodes 57kDa, one of the most critical drug-metabolizing enzymes, responsible for the biotransformation of 30–50% of clinically used drugs [18, 19]. The promoter variant CYP3A4*1B (g.392A>G, rs2740574) has been associated with increased transcriptional activity [20]. Consequently, this allele has been linked to altered taxane pharmacokinetics and increased clearance [21], with some studies suggesting it contributes to the risk of severe taxane-induced neuropathy [22]. In lung cancer, CYP3A4*1B has been reported in one case-control study to be associated with an increased risk of small-cell lung cancer and with smoking-related lung cancer risk, while a conference abstract suggested a higher frequency of CYP3A4*1B in NSCLC compared with the general population. However, these findings should be interpreted cautiously, as the functional significance of CYP3A4*1B remains controversial and current evidence does not establish a causal role for this variant in lung carcinogenesis [23, 24]. Moreover, Subhani *et al.* [25] investigated CYP3A4*1B and CYP3A5*3 in a South Indian lung cancer cohort in the context of paclitaxel therapy, raising the possibility that CYP3A variation may influence taxane handling.

CYP2C8, located at 10q23.33, spans ~31 kb, contains 9 exons, and encodes a 490-amino-acid enzyme. CYP2C8 is involved in the metabolism of approximately 5% of clinically used drugs. Importantly, CYP2C8*3 is not defined by a single variant, but by a haplotype comprising two missense substitutions, CYP2C8 c.416G>A (p.Arg139Lys, rs11572080) and CYP2C8 c.1196A>G (p.Lys399Arg, rs10509681) [26]. Bahadur *et al.* [27] reported that liver microsomes from carriers of the CYP2C8*3 allele exhibited significantly lower paclitaxel 6 α -hydroxylase activity than wild-type samples, suggesting reduced paclitaxel metabolism *in vitro*. However, the functional effect of CYP2C8*3 appears to be substrate-dependent rather than uniformly decreased across all CYP2C8 substrates [28].

Regarding transport, ABCG2 is a key mediator of clinically significant drug-drug interactions (DDIs) [29]. ABCG2 (BCRP) (4q22.1) spans 66 kb and encodes a 655-amino-acid enzyme, ~72 kDa protein. The ABCG2 c.421C>A (Q141K) variant results in decreased protein expression due to impaired folding and trafficking, thereby reducing efflux capacity and altering drug disposition [30]. A recent study showed that the ABCG2 transporter might be a potential target for preventing paclitaxel therapy failure [31].

Despite the established role of these polymorphisms, most pharmacogenetic research has have investigated their impact in breast and ovarian cancers. Consequently, data on their impact in lung cancer remain limited.

Furthermore, there is a need to clearly distinguish these germline (constitutional) variants from somatic

mutations (e.g., *EGFR*, *KRAS*) directly involved in carcinogenesis. In contemporary pathology practice, tumor molecular profiling and germline pharmacogenetic data are increasingly viewed as complementary components of precision medicine. Within this context, our study supports the potential value of germline pharmacogenetic testing alongside histopathological characterization, particularly for anticipating treatment-related toxicity rather than predicting intrinsic tumor sensitivity. As pathologists increasingly participate in integrated diagnostic workflows combining morphological and molecular data, the investigation of germline pharmacogenetic markers within histologically characterized lung cancer populations becomes especially relevant.

Accordingly, the aim of this study was to evaluate the impact of *CYP3A4*1B* (g.392A>G), *CYP2C8* (c.416G>A), and *ABCG2* (c.421C>A) polymorphisms on taxane treatment outcomes in a histologically defined lung cancer cohort. By examining the relationship between these germline variants, therapeutic response, and adverse events, we aim to provide evidence for individualized strategies that complement existing tumor profiling, ultimately maximizing therapeutic benefit while minimizing toxicity.

Material and methods

Population study

This is a pharmaco-epidemiological, retrospective study conducted at oncology centers in Oran, Algeria (Oncology Department of the Hospital-University Establishment 1st Novembre). The study period extended from July 27, 2023, to September 27, 2024. All patients were informed of the study purpose and provided both verbal and written consent.

Data collection

A total of 110 patients with lung cancer from Western Algeria were enrolled. Eligibility was limited to patients receiving taxane-based chemotherapy. Demographic and clinical data included gender, age, medical history, cancer type, stage of cancer, treatment frequency, dosage and clinical response. Treatment adverse events, with a specific focus on peripheral neuropathy, were systematically divided into five categories such as general, gastrointestinal, respiratory, dermatological, and neurological.

Data stratification

To evaluate treatment response, patients were classified into two groups according to the response evaluation criteria in solid tumors [32]: a responder group, disease stability, partial response, or complete response to treatment, and a non-responder group, defined by tumor progression.

Independently, taxane induced toxicities were evaluated using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0, 2017): patients were divided into two severity-based groups: Group 1 (Grades 1–2) and Group 2 (Grades 3–4).

Histopathological diagnosis and classification

Histological subtyping followed standard clinical pathology protocols. Tumors were categorized as adenocarcinoma, squamous cell carcinoma (designated as epidermoid carcinoma in local pathology reports), or other histological types (including large cell neuroendocrine carcinoma and unspecified NSCLC). For unresectable metastatic cases, diagnosis was established *via* small biopsy specimens obtained from patients with unresectable metastatic lung tumors. Diagnostic material was derived from bronchoscopic biopsies in 47 cases and transthoracic (transparietal) biopsies in 63 cases. A standard immunohistochemical panel (TTF1, P40, CK5/6) was systematically applied to support subtype assignment and to distinguish squamous from non-squamous tumors. Data regarding specific diagnostic procedures and tumor-nodes-metastasis staging (8th edition) were also recorded.

Genotypes analysis

Venous blood samples (5 ml) were collected in EDTA tubes for DNA genomic extraction. The DNA was isolated from whole blood samples of all 110 patients using the salting-out method [33] and diluted to a final concentration of 10 ng/μl in 1× Tris/EDTA buffer (pH 7.5).

The *CYP2C8* c.416G >A, *CYP3A4* g.392A>G and the *ABCG2* c.421C>A polymorphisms were assessed using TaqMan® SNP Genotyping Assays: *CYP2C8*, rs11572080: C_25625794_60, *CYP3A4*, rs2231142: C_1837671_50 and *ABCG2*, rs223114: C_15854163_70 (VIC/FAM) and Applied Biosystems TaqPath™ Pro-Amp™ Master Mix in the QuantStudio™ 5 instrument by ThermoFisher Scientific. Thermal cycling conditions consisted of 60°C for 30 seconds, 95°C for 10 minutes, 40 cycles of 95°C for 15 seconds and 60°C for 1 minute, and a final step at 60°C for 30 seconds.

Statistical analysis

Continuous variables are reported as means ± standard deviation, while categorical variables are presented as frequencies and percentages. Qualitative data comparisons were performed using χ^2 tests (Epi Info™ version 7), or Fisher's exact test was applied when appropriate. Statistical significance was defined as a *p*-value < 0.05. Allelic and genotypic risks were evaluated through odds ratios (OR) with corresponding 95% CI.

The study employed R software *via* the RStudio interface to perform a one-way analysis of variance (ANOVA) for comparing taxane doses across *CYP2C8* c.416G>A and *ABCG2* c.421C>A genotypes. Further-

more, SPSS software was used to conduct an ANOVA test for the *CYP3A4* g.392A>G polymorphism. In order to obtain more robust insights, an ordinal logistic regression model (logit link) was also implemented in SPSS, with the neuropathy grade as a dependent variable and the *CYP3A4* genotype as the principal predictor.

To determine whether the studied polymorphisms were independently associated with treatment outcomes, multivariate logistic regression analyses were performed. The effects of *CYP3A4* g.392A>G, *CYP2C8* c.416G>A, and *ABCG2* c.421C>A genotypes were evaluated after adjustment for histological subtype and taxane dose. Wild-type genotypes were used as reference categories. Separate regression models were fitted for treatment response and peripheral neuropathy. Threshold parameters of the model were not interpreted as they lack direct clinical relevance.

Results

Clinical and demographic description

Analysis of the clinical and demographic characteristics of 110 patients based on their responder status revealed that histological subtype, body surface area

(BSA), and paclitaxel dosage were significantly associated with treatment response (Table I). Squamous cell carcinoma was strongly associated with favorable treatment response compared to adenocarcinoma (OR = 0.1 [0.04–0.78], $p = 0.01$), and BSA >1.7 m² was significantly associated with higher response rates (OR = 0.42 [0.19–0.91], $p = 0.04$). Additionally, paclitaxel at a dose of 90 mg/m² was significantly associated with improved response compared to 80 mg/m² (OR = 0.28 [0.09–0.88], $p = 0.05$). A trend toward poorer response was observed in patients with an advanced nodal stage (N2–N3) compared to N0–N1 (OR = 2.08 [0.96–4.53], $p = 0.09$). In contrast, other clinical and demographic variables including age, sex, tumor stage, presence of chronic diseases, and frequency of treatments were not significantly associated with therapeutic response. Regarding treatment regimens, 22 patients received docetaxel as monotherapy, while four received a combined cisplatin therapy. The majority of patients (84) were treated with a paclitaxel and carboplatin combination. To optimize the patient management, some patients received adjunctive therapies: 12 patients were administered zoledronic acid (Zometa), 10 received bevacizumab, and 3 patients underwent combined chemimmunotherapy with pembrolizumab. These findings

Table I. Demographic and clinical data distribution regarding the response to taxane's chemotherapy

PARAMETERS	ALL PATIENTS (N = 110)	RESPONDER PATIENTS (%)	NON-RESPONDER PATIENTS (%)	P-VALUE	OR (95% CI)
Gender					
Male	105 (95.45)	42 (93.33)	63 (96.92)	1 ^a	
Female	5 (4.54)	3 (6.66)	2 (3.07)	0.33	0.44 (0.07–2.77) ^b
Age [years]					
< 60	51 (46.36)	23 (20.90)	28 (43.07)	1 ^a	
≥ 60	59 (53.63)	22 (48.88)	37 (56.92)	0.52	1.38 (0.62–2.96)
BSA [m ²]					
≤ 1.7	59 (53.63)	19 (42.22)	40 (61.53)	1 ^a	
> 1.7	51 (46.36)	27 (60)	24 (36.92)	0.04*	0.42 (0.19–0.91)
Clinical stage					
III	43 (39.9)	15 (33.33)	28 (43.07)	1 ^a	
IV	67 (60.90)	30 (66.66)	37 (56.92)	0.40	0.66 (0.29–1.45)
T-stage					
T0–T2	21 (19.09)	10 (22.22)	11 (16.92)	1 ^a	
T3–T4	89 (80.90)	35 (77.377)	54 (83.07)	0.65	1.40 (0.53–3.64)
N-stage					
N0–N1	47 (42.72)	24 (53.33)	23 (35.38)	1 ^a	
N2–N3	63 (57.27)	21 (46.66)	42 (64.61)	0.09	2.08 (0.96–4.53)
M-stage					
M0	41 (37.27)	16 (35.55)	25 (38.46)	1 ^a	
M1	69 (62.72)	29 (64.44)	40 (61.53)	0.91	0.88 (0.40–1.94)

Cancer type					
Adenocarcinoma	81 (73.63)	30 (66.66)	51 (78.46)	1 ^a	
Squamous cell carcinoma	12 (10.90)	9 (20)	3 (4.61)	0.01*	0.1 (0.04–0.78) ^a
Others	17 (15.45)	5 (11.11)	12 (18.46)	0.38	1.4 (0.45–4.39)
Chronic disease					
No	72 (65.45)	27 (60)	45 (69.23)	1 ^a	
Yes	38 (34.54)	18 (40)	20 (30.76)	1	0.66 (0.30–1.47)
Paclitaxel [mg/m ²]					
80	47 (42.72)	18 (40)	29 (44.61)	1 ^a	
90	19 (17.27)	13 (28.88)	6 (9.23)	0.05*	0.28 (0.09–0.88)
200	18 (16.36)	7 (15.55)	11 (16.92)	1	0.97 (0.31–2.97)
Docetaxel [mg/m ²]					
75	8 (7.27)	1 (2.22)	7 (10.76)	1 ^a	
135	6 (5.45)	2 (4.44)	4 (6.15)	0.38	0.28 (0.01–4.23) ^b
175	12 (10.90)	5 (11.11)	7 (10.76)	0.18	0.2 (0.01–2.18) ^b
Chemotherapy frequency					
Weekly	74 (67.27)	32 (71.11)	42 (64.61)	1 ^a	
3 weeks	36 (32.72)	14 (31.11)	22 (33.84)	0.81	1.19 (0.5–2.69)

BSA – body surface area, M-stage – metastasis stage, N-stage – node stage, OR – odds ratio, T-stage – tumor stage

^a Reference category

^b Fisher's exact test

* Significant association

illustrate the diversity of therapeutic strategies employed and their potential impact on clinical outcomes.

The most commonly reported adverse events recorded were fatigue, gastrointestinal disorders (such as anorexia and diarrhea), cough, and alopecia (Table II) which align with the established toxicity profiles of taxane-based chemotherapies. While less frequent, neurological and respiratory effects were also observed, necessitating close monitoring. Early management of adverse effects is crucial for maintaining quality of life and therapeutic adherence.

No significant correlation was observed between treatment response and the occurrence of Grade I neuropathy (Table III). Similarly, no significant differences were found for more severe neuropathies (G2–G3).

Histological subtype and treatment response

Adenocarcinoma was the predominant histology ($n = 81$, 73.6%), followed by squamous cell carcinoma ($n = 12$, 10.9%) and other types ($n = 17$, 15.5%). Univariate analysis revealed that squamous cell carcinoma was significantly associated with favorable treatment response compared to adenocarcinoma (OR = 0.1 [0.04–0.78], $p = 0.01$) (Table I). Patients with squamous cell carcinoma, as well as those who received paclitaxel at a dose of 90 mg/m², showed significantly higher response rates, likely reflecting both intrinsic tumor biology and treatment selection patterns. Squamous cell carcinoma

may exhibit differential sensitivity to taxane-based regimens, or this association may reflect confounding by performance status or smoking history. Importantly, our data support the notion that histopathological classification remains a critical determinant of chemotherapy outcomes, independent of host pharmacogenetic variants.

Molecular characterization

Epidermal growth factor receptor mutation testing was performed in a subset of patients. However, routine access was limited in the public sector during the study period. Among the 26 patients with available EGFR results, 18 (69.2%) harbored wild-type EGFR, while 8 (30.8%) presented EGFR alterations including 2 exon 18 mutations, 5 exon 19 deletions, and 1 exon 20 insertion. Additional biomarker testing was limited: PD-L1 expression was reported in 8 patients (7 negative, 1 positive), ALK rearrangement in 2 patients (both negative), and ROS1 rearrangement in 1 patient (positive).

The CYP2C8, CYP3A4 and ABCG2 polymorphism analysis regarding the response to taxane treatment

The results of this study indicate that neither the CYP2C8 c.416G>A nor the ABCG2 c.421C>A host genetic

Table II. Distribution of patients with lung cancer according to taxane chemotherapy's related side effects

PARAMETERS	SIDE EFFECTS	ALL PATIENTS, <i>N</i> = 110 (%)
General	Asthenia	68 (61.81)
	Fatigue	100 (90.90)
	Diaphoresis	10 (9.09)
	Headache	22 (20)
Gastrointestinal	Anorexia	45 (40.90)
	Diarrhea	38 (34.54)
	Nausea	23 (20.90)
	Constipation	27 (24.54)
	Vomiting	26 (23.63)
	Stomatitis	23 (20.90)
	Mucositis	16 (14.54)
Neurological	Insomnia	27 (24.54)
	Dizziness	27 (24.54)
	Memory impairment	6 (5.45)
	Balance disorder	11 (10)
	Visual disturbances	11 (10)
Respiratory	Dyspnea	23 (20.90)
	Cough	60 (54.54)
	Hemoptysis	9 (8.18)
Dermatologic	Alopecia	36 (32.72)
	Allergy	15 (13.63)

Table III. Peripheral neuropathy grades' distribution regarding the response to taxane chemotherapy

NEUROPATHY GRADE	ALL PATIENTS, <i>N</i> = 110 (%)	RESPONDER PATIENTS (%)	NON-RESPONDER PATIENTS (%)	<i>P</i> -VALUE	OR (95% CI)
G0	43 (39.09)	17 (37.77)	26 (40)	1 ^a	
G1	58 (52.72)	25 (55.55)	33 (50.76)	0.87	0.86 (0.38–1.92)
G2	5 (4.54)	1 (2.22)	4 (6.15)	1 ^a	
G3	4 (3.63)	2 (4.44)	2 (3.07)	0.4	0.25 (0.01–4.72) ^b

G0 – grade 0 (no neuropathy), G1 – grade 1 (mild neuropathy), G2 – grade 2 (moderate neuropathy), G3 – grade 3 (severe neuropathy)

^a Reference category

^b Fisher's exact test

polymorphism was significantly associated with taxane therapy response in patients with lung cancer (Table IV).

Analysis of these genotypes across neuropathy severity groups (Table V) showed no significant taxane-induced peripheral neuropathy suggesting that these variants do not influence neurological tolerance to therapy.

In contrast, the evaluation of taxane-induced toxicity using ordinal logistic regression (logit link) revealed a significant association with the CYP3A4 g.392A>G polymorphism. Compared with the AA genotype as the reference, carriers of the GA genotype had a significantly higher risk of more severe neuropathy ($\beta = 1.179$; OR = 3.25, 95% CI: 1.45–7.29, $p = 0.004$).

Conversely, the GG genotype showed no significant association with neuropathy severity ($\beta = 0.499$; $p = 0.556$; OR » 1.65; 95% CI: 0.31–8.67).

In the multivariate analysis adjusting for histology and dose, only 98 patients with complete data for all three polymorphisms were included. Among this subset, only the CYP3A4 GA genotype was significantly associated with treatment outcomes. Specifically, carriers of the GA genotype had a three-fold increased risk of neuropathy compared with the AA wild-type (OR 3.15, 95% CI: 1.24–8.47, $p = 0.018$) (Table VI). No genetic polymorphisms, including variants in CYP3A4, CYP2C8, or ABCG2, were signifi-

Table IV. The *CYP2C8 c.416G>A* and *ABCG2 c.421C>A* polymorphism distribution according to the response to taxane chemotherapy

PARAMETERS	ALL PATIENTS, N = 110 (%)	RESPONDER PATIENTS (%)	NON-RESPONDER PATIENTS (%)	P-VALUE	OR (95% CI)
CYP2C8 c.416G>A rs11572080	103 (93.63)	45 (100)	58 (89.23)	–	–
Genotypes					
GG	76 (69.09)	31 (68.88)	45 (69.23)	1 ^a	
GA	24 (21.81)	12 (26.66)	12 (23.52)	0.57	0.68 (0.27–1.73)
AA	3 (2.72)	2 (4.44)	1 (1.96)	0.37	0.34 (0.02– 3.96) ^b
Allele					
G	176 (97.12)	74 (82.22)	102 (87.93)	1 ^a	
A	30 (13.63)	16 (17.77)	14 (12.06)	0.34	0.63 (0.29–1.38)
ABCG2 c.421 C>A rs2231142	101 (91.81)	52 (96.29)	49 (96.07)	–	–
Genotypes					
CC	90 (81.81)	44 (81.48)	46 (90.19)	1 ^a	–
CA	11 (10)	8 (14.81)	3 (5.88)	0.11	0.35 (0.08–1.43) ^b
AA	0	0	0	0	0
Allele					
C	191 (86.81)	96 (88.88)	95 (93.13)	1 ^a	
A	11 (5)	8 (7.40)	3 (2.94)	0.12	0.37 (0.09– 1.47) ^b
CYP3A4 g.392A>G rs2740574	106 (96.36)	45 (100)	61 (93.84)	–	–
Genotypes					
AA	50 (45.45)	22 (48.88)	28 (47.07)	1 ^a	
AG	50 (45.45)	19 (42.22)	31 (47.69)	0.68	1.28 (0.57–2.84)
GG	6 (5.45)	4 (8.88)	2 (3.07)	0.26	0.39 (0.06–2.34) ^b
Allele					
A	150 (68.18)	63 (70)	87 (66.92)	1 ^a	
G	62 (28.18)	27 (30)	35 (26.92)	0.95	0.93 (0.51–1.70)

^a Reference category

^b Fisher's exact test

Table V. The *CYP3A4 g.392A>G*, *CYP2C8 c.416G>A* and *ABCG2 c.421C>A* polymorphism distribution according to neuropathy grade

PARAMETERS	NEUROPATHY GRADE		P-VALUE	OR (95% CI)
	G0 + G1	G2 + G3		
CYP2C8 c.416G>A rs11572080, N = 103	93 (90.29)	10 (9.70)		
Genotypes				
GG	68 (66.01)	7 (6.79)	1 ^a	
GA	23 (22.33)	2 (1.94)	0.6	0.84 (0.16–4.35) ^b
AA	2 (1.94)	1 (0.97)	0.28	4.85 (0.38–60) ^b
Allele				
G	159 (77.18)	16 (7.76)	1 ^a	
A	27 (13.10)	4 (1.94)	0.35	1.47 (0.45–4.73) ^b
ABCG2 c.421 C>A rs2231142, N = 101	92 (91.08)	9 (8.91)		
Genotypes				
CC	83 (82.17)	8 (7.92)	1 ^a	
CA	9 (8.91)	1 (0.99)	0.62	1.15 (0.12–10.29) ^b
AA	0	0	0	0

Table V. Cont.

Allele				
C	175 (86.63)	17 (8.41)	1 ^a	
A	9 (4.45)	1 (0.49)	0.61	1.14 (0.13–9.57) ^b
CYP3A4 g.392 A>G rs2740574, N = 106	97 (91.50)	9 (8.49)		
Genotype				
AA	50 (47.16)	0	1 ^a	
AG	41 (38.67)	9	0.001	–1 (2.87 to –1) ^b
GG	6 (5.66)	0	10–8	–1 (15.54 to –1) ^b
Allele				
A	141 (66.50)	9 (4.24)	1 ^a	
G	53 (25)	9 (4.24)	0.07	2.66 (1–7.06)

^a Reference category^b Fisher's exact test

OR not estimable because one cell in the contingency table equals 0; exact 95% CI based on Mid-P.

Table VI. Multivariate analysis of pharmacogenetic and clinical predictors of taxane treatment efficacy and neurotoxicity

SINGLE NUCLEOTIDE POLYMORPHISM SNP	CATEGORY	N (%)	RESPONSE OR (95% CI)	RESPONSE P-VALUE	NEUROPATHY OR (95% CI)	NEUROPATHY P-VALUE
CYP3A4 g.392A>G	AA	49 (50.0)	1.00 ^a	–	1.00 ^a	–
	AG	44 (44.9)	0.51 (0.20–1.24)	0.14	3.15 (1.24–8.47)	0.018
	GG	5 (5.1)	2.05 (0.25–20.64)	0.51	5.95 (0.64–137.99)	0.16
CYP2C8 c.416G>A	GG	73 (74.5)	1.00 ^a	–	1.00 ^a	–
	GA	22 (22.4)	0.99 (0.34–2.86)	0.98	0.95 (0.31–2.96)	0.93
	AA	3 (3.1)	3.58 (0.31–82.54)	0.32	–	0.99
ABCG2 c.421C>A	CC	87 (88.8)	1.00 ^a	–	1.00 ^a	–
	CA	11 (11.2)	2.57 (0.63–12.34)	0.20	2.16 (0.53–10.48)	0.30
Histology	Adenocarcinoma	70 (71.4)	2.79 (0.79–11.69)	0.13	1.76 (0.50–6.19)	0.37
	Squamous cell carcinoma	12 (12.2)	3.27 (0.60–20.08)	0.18	1.04 (0.18–6.17)	0.97
	Other NSCLC	16 (16.3)	1.00 ^a	–	1.00 ^a	–
Dose [mg]	–	–	1.00 (0.99–1.01)	0.78	1.00	–

SNP – single nucleotide polymorphism, NSCLC – non-small cell lung cancer

^a Reference categoryBold indicates statistical significance ($p < 0.05$), total N = 98.

cantly associated with treatment response. Histological subtype and chemotherapy dose similarly did not predict efficacy or toxicity in this cohort.

The ABCG2 c.421C>A polymorphisms and taxane dose

Analysis of taxane dosing by the ABCG2 c.421C>A genotype revealed significant differences between

groups. Patients with the heterozygous CA genotype received significantly lower mean taxane doses than those with the homozygous CC genotype ($p = 0.032$) (Figure 1). These results suggest that carriers of the A allele may have increased sensitivity to taxane toxicity, leading to dose adjustments to reduce adverse effects. While these findings highlight the impact of the

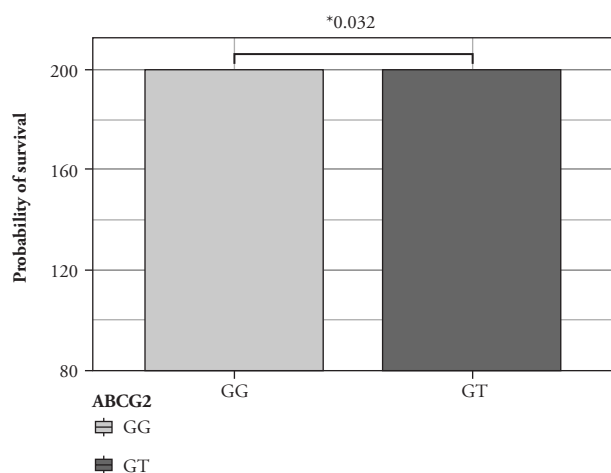


Figure 1. The *ABCG2* c.421C>A polymorphism distribution according to taxane dose

* Significant

ABCG2 genotype on taxane tolerance, larger studies are needed to confirm its role in guiding personalized treatment strategies.

Discussion

Although surgery and radiation therapy are the main treatments for NSCLC, chemotherapy significantly improves survival in patients diagnosed at advanced stages [34]. However, resistance to cytotoxic agents remains a critical challenge [35]. Paclitaxel, while effective in disrupting microtubule dynamics, frequently leads to resistance following prolonged therapy, resulting in a poor prognosis [36, 37].

Body surface area greater than 1.7 m² was associated with a better response rate ($p = 0.04$, OR 0.42, 95% CI: 0.19–0.91). This finding aligns with the pharmacokinetic rationale of taxane dosing, which is traditionally calculated based on BSA [38]. Although BSA-based dosing does not always reduce interindividual exposure variability, a recent work emphasizes the importance of dose individualization beyond surface area calculations, particularly through therapeutic drug monitoring [38]. A recent systematic review also demonstrated that body composition, including lean body mass, significantly influences toxicity of taxane-based chemotherapy regimens [39], suggesting that anthropometric parameters remain relevant determinants of efficacy and tolerability.

Squamous cell carcinoma was significantly associated with better response compared to adenocarcinoma ($p = 0.01$, OR 0.10, 95% CI: 0.04–0.78). This observation is consistent with literature suggesting differences in taxane sensitivity according to NSCLC histological subtypes. The Eastern Cooperative Oncology Group 1594 study established that squamous cell carcinoma exhibited particular responsiveness to taxane-based combinations, a pattern attributed

to distinct proliferative indices and apoptotic thresholds [40]. Recent advances in understanding molecular mechanisms have further illuminated this histology-specific sensitivity, highlighting signaling pathways such as DSTYK inhibition, which particularly sensitize squamous cell carcinoma cells to taxane-based treatments [41].

In our study, the *CYP2C8* c.416G > A polymorphism was not associated with taxane response in Algerian patients with NSCLC. Only a few studies have investigated the relationship between this polymorphism and taxane treatment outcomes in lung cancer. In the U.S. population, the *CYP2C8* rs11572080 variant has also been linked to an increased risk of diarrhea [42]. Most studies have focused on the impact of the *CYP2C8* variants on taxane treatment in other cancers, particularly, breast and ovarian cancer [43, 44].

However, *CYP2C8* is considered as the major enzyme involved in paclitaxel metabolism [45, 46]. The *CYP2C8**3 allele has been correlated with reduced paclitaxel metabolism in both *in vitro* and *in vivo* studies [47, 48]. According to several studies, individuals with *CYP2C8* gene variants linked to decreased enzymatic activity, particularly, the *CYP2C8**3 allele show slower paclitaxel clearance, which may raise the risk of treatment-induced peripheral neuropathy [46, 49]. In another cohort, this allele defined by the rs10509681 and rs11572080 variants, has been associated with reduced enzymatic activity with most carriers classified as intermediate or poor metabolizers [50]. This genotype results in two nonsynonymous mutations (R139K and K399R) and has been linked to a reduction in the metabolic activity of paclitaxel *in vitro* [47, 51].

In our study, there is no correlation between the *ABCG2* c.421 C>A variant and taxane chemotherapy outcome in Algerian patients with NSCLC. The same results were shown on Indian [52], and Germany populations [53].

Previous studies have demonstrated that the *ABCG2* transporter's expression and function influence paclitaxel sensitivity [54, 55]. Recent research suggests that targeting the *ABCG2* transporter might help reduce paclitaxel treatment resistance [31]. The *ABCG2* transporter's overexpression decreases docetaxel's intracellular accumulation, thereby increasing drug resistance. In contrast, targeted suppression of *ABCG2* by siRNA enhances cytotoxic effects by restoring tumor cells' sensitivity [56, 57]. According to Schiller *et al.* [40], after adjusting for age and treatment cycles, a significant correlation was found between the *ABCG2* rs2231142 polymorphism and treatment-related toxicities, particularly thrombocytopenia ($p = 0.045$). This nonsynonymous variant is known to decrease *ABCG2* expression and drug efflux capacity [40]. A study involving 1004 patients with NSCLC investigated host genetic polymorphisms in the *ABCG2* gene, and showed that many variants, such as rs2231142, were associated with treatment response. However, this study

focused on platinum-based chemotherapy, rather than taxane-specific effects [58].

Our finding that the *CYP3A4* g.392A>G polymorphism is associated with higher grades of taxane-induced peripheral neuropathy in West Algerian lung cancer patients is consistent with previous pharmacogenetic studies implicating reduced-function *CYP3A4* alleles in taxane neurotoxicity. Notably, de Graan *et al.* [59] reported that carriers of *CYP3A4**22 exhibited a significantly increased risk of severe paclitaxel-induced neurotoxicity across two independent cohorts. Using whole-exome sequencing, a study by Apellániz-Ruiz *et al.* [60] subsequently identified rare loss-of-function *CYP3A4* variants predictive of paclitaxel dose-limiting neuropathy. In breast cancer, Kus *et al.* [22] demonstrated that a common *CYP3A4* polymorphism conferred an elevated risk of $\geq$ Grade 2 neuropathy in patients treated with either paclitaxel or docetaxel. More recently, Alvarado *et al.* [61] reviewed accumulating evidence supporting *CYP3A4**20 and *CYP3A4**22 as candidate biomarkers of taxane-induced peripheral neuropathy, while underscoring the need for larger and ethnically diverse cohorts. Although a systematic review and meta-analysis by McEvoy *et al.* [21] suggested that the overall contribution of the *CYP3A* variation to taxane neurotoxicity is modest at the population level, our findings extend this body of work by demonstrating a significant *CYP3A4*-related neuropathy risk signal in a North African lung cancer cohort, thereby supporting further evaluation of *CYP3A4* variants within multigene risk models for taxane-induced neuropathy.

The observation that *CYP3A4* heterozygosity may increase neuropathy risk is consistent with its known role of *CYP3A4* as the primary enzyme involved in taxane metabolism and clearance [62]. Reduced *CYP3A4* activity, often linked to variant alleles, can prolong systemic exposure to neurotoxic metabolites and thereby predisposing patients to peripheral neuropathy [63]. Although previous studies have reported inconsistent findings regarding *CYP3A* polymorphisms and taxane-related outcomes, our cohort did not show such associations. This may suggest that, in addition to pharmacokinetic variability, pharmacodynamic factors, such as β -tubulin-related mechanisms, could also contribute to differences in treatment efficacy [64]. These retrospective findings indicate that *CYP3A4* genotyping may help to identify patients at increased risk of taxane-induced neurotoxicity; however, the available evidence is inconsistent, and prospective validation is required before clinical application [22].

To our knowledge, this is the first pharmacogenetic study of taxane metabolism in Algerian lung cancer patients. Comparison with recent gnomAD v4 and 1000 Genomes data reveals distinct allele frequencies in our cohort: the *CYP3A4* g.392A>G variant (rs2740574) had a frequency of 28.2%, which is inter-

mediate between European populations (approximately 2.8–3.5%) and African-ancestry populations (approximately 23.4–35.9%) [65]. The *CYP2C8* c.416A allele (rs11572080) was observed at 13.6% aligning with European rates (11.8%) but is lower than those reported for the West African population (> 16%) [66]. Similarly, the *ABCG2* c.421A allele (rs2231142) was present at 5.0%, which is comparable to Middle Eastern and European populations (3–10%) but much lower than East Asian levels (approximately 30%) [67]. These findings underscore the unique genetic architecture of this underrepresented North African population and highlight the necessity of region-specific pharmacogenetic data for precision medicine.

Although our study has several limitations, these do not diminish the relevance of the observed findings. The relatively small sample size may have reduced the statistical power to detect weaker associations and limits the generalizability of the results; however, the significant associations identified remain of interest and warrant further investigation in larger cohorts. In addition, the heterogeneity of treatment regimens may have contributed to differences in toxicity profiles and should be considered when interpreting adverse-event analyses. Likewise, the observed associations may have been influenced, at least in part, by histological subtype biology, treatment selection, and subgroup distribution. Nevertheless, these factors do not undermine the overall value of our results, which provide preliminary evidence supporting the role of host pharmacogenetic variability in taxane-related toxicity. Future studies in larger and more homogeneous populations, including a broader range of genetic polymorphisms, are needed to confirm and extend these findings.

Conclusions

This study is the first to explore the association of *CYP3A4* g.392A>G, *CYP2C8* c.416G>A, and *ABCG2* c.421C>A polymorphisms with taxane treatment outcomes in Algerian patients with lung cancer. The observed association between *ABCG2* genotypes and cumulative taxane exposure, as well as the relationship between the *CYP3A4* variant and higher grades of taxane-induced peripheral neuropathy, suggests that host pharmacogenetic variability may contribute to interindividual differences in treatment tolerance. Although these findings should be interpreted with appropriate caution, they provide population-specific evidence that may help refine current understanding of taxane-related toxicity. Beyond their immediate clinical implications, these results may also serve as a basis for future investigations into additional genetic and molecular factors involved in chemotherapy response and adverse events in lung cancer. Overall, our data support the notion that pharmacogenetics may play a meaningful role in individualizing treatment and could contribute to the

development of more tailored and better-tolerated therapeutic strategies.

Disclosures

1. Institutional review board statement: This study was approved by the Ethics Committee of the Research Laboratory of Toxicology, Environment, and Health at the University of Sciences and Technology of Oran Mohamed Boudiaf (approval decision no. 001/LATES/Usto/2023, dated: 2023).
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