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Short Communication

Association of *ABCB1* genotypes with paclitaxel-mediated peripheral neuropathy and neutropenia ☆

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ABSTRACT

Here, we evaluated the relationships between *ABCB1* (P-glycoprotein, MDR1) polymorphisms and paclitaxel (Taxol)-induced toxicity and pharmacokinetics. Twenty-six patients were assessable for pharmacogenetics and pharmacokinetics, 22 for neurotoxicity and 18 for myelotoxicity. Patients carrying two reference alleles for the *ABCB1* 3435C > T polymorphism trended toward a reduced risk to develop neuropathy as compared to patients carrying at least one variant allele ($P = 0.09$). Additionally, patients who were homozygous variant at the 2677 and 3435 loci had a significantly greater percent decrease in absolute neutrophil count at nadir ($P = 0.02$). Neither polymorphism correlated with paclitaxel pharmacokinetics. This pilot study suggests that paclitaxel-induced neuropathy and neutropenia might be linked to inherited variants of *ABCB1* through a mechanism that is unrelated to altered plasma pharmacokinetics.

1. Introduction

One of the primary proteins involved in paclitaxel elimination and distribution is ABCB1 (P-glycoprotein; MDR1).[1,2] ABCB1 is expressed in several tissues, including the blood–brain barrier,[3] and haematopoietic precursor cells.[4] Although ABCB1 has not been detected in peripheral nerve cells, the cells that make up the blood–nerve barrier express ABCB1 and are thought to protect the peripheral nervous tissue by transporting toxic substances from the nervous system back into the systemic circulation.[5]

There are three common single nucleotide polymorphisms (SNPs) in *ABCB1* that have been associated with altered ABCB1 expression, and that have profound implications in the pharmacokinetics and pharmacodynamics of various drugs.[6] These include the synonymous 1236C > T, the non-synonymous 2677G > T/A (Ala893Ser/Thr), and the synonymous 3435C > T SNPs. Animal models have indicated that transduction of haematopoietic cells with human *ABCB1* could protect from severe paclitaxel-induced myelotoxicity.[7] Based on differential expression, those patients with low-expressing *ABCB1* genetic variants could be more likely to experience

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paclitaxel-induced peripheral neuropathy and neutropenia. Therefore, we investigated the association of *ABCB1* genetic variants with the incidence and severity of these side effects in patients treated with paclitaxel.

2. Patients and methods

2.1. Study design and patients

Patients with advanced solid tumours were treated with weekly, single-agent paclitaxel (Taxol), administered as a 1- or 3-h infusion. All patients provided written informed consent and the study was approved by the local ethics committee. Eligibility criteria, treatment schedules, and assessment of pharmacokinetic and toxicity profiles have been described previously.[8,9] The original clinical trial was supported by investigator-initiated grants from Bristol-Myers-Squibb, Munich, Germany. The current analysis was approved by the review board of the National Cancer Institute.

2.2. *ABCB1* genotype analysis

Polymerase chain reaction (PCR) was performed using the Platinum Taq PCR Kit from Invitrogen (Carlsbad, CA, USA). Direct nucleotide sequencing PCR was conducted using the Big Dye Terminator Cycle Sequencing Ready Reaction kit V3.1 (Applied Biosystems, Foster City, CA, USA) and an ABI Prism 310 Genetic Analyzer.

2.3. Statistical considerations

Associations of variant genotypes with neutropenia and individual pharmacokinetic parameters were evaluated statistically with a Kruskal–Wallis test or an exact Wilcoxon rank sum test after a Bonferroni adjustment. The probability of the development of peripheral neuropathy was analysed using the Kaplan–Meier method,[10] with an exact log-rank test.[11] All *P* values are two-tailed, and $P < 0.05$ was considered to reflect statistical significance.

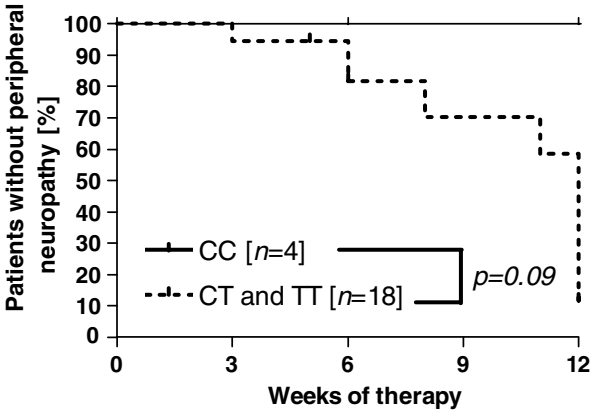

Fig. 1 – Association between risk of peripheral neuropathy and *ABCB1* 3435C > T genotype status in 22 patients. CC – *ABCB1* 3435-CC genotype; CT – *ABCB1* 3435-CT genotype; TT – *ABCB1* 3435-TT genotype. The *P* value was obtained from an exact two-tailed log-rank test.

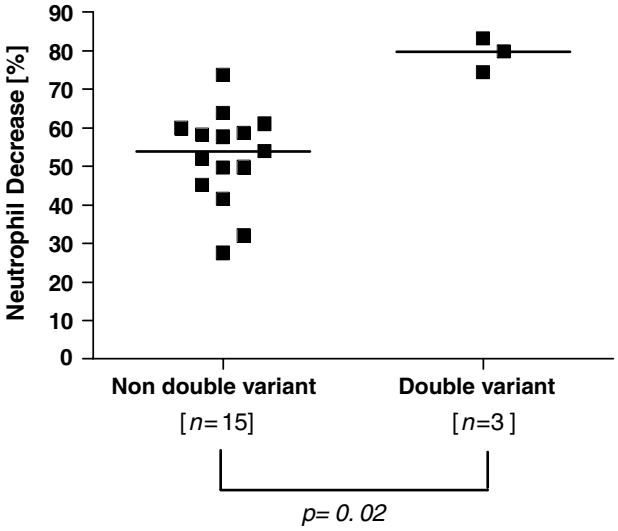

Fig. 2 – Association between ANC and *ABCB1* 2677G > T and 3435C > T genotype status in 18 patients. Non double variants – for both *ABCB1* 2677G > T and *ABCB1* 3435C > T alleles; Double variants – for both *ABCB1* 2677G > T and *ABCB1* 3435C > T alleles. The unadjusted *P* value was 0.0025.

3. Results

None of the patients carrying the reference allele for the *ABCB1* 3435C > T transition developed peripheral neuropathy during their observation period, whereas patients carrying at least one variant allele trended toward an increased risk for developing peripheral neuropathy ($P = 0.09$; Fig. 1).

Patients carrying variants at both the 2677 and 3435 loci demonstrated a 1.5-fold greater percent decrease ($P = 0.02$) in absolute neutrophil count at nadir (median, 79.7%; range, 74.2– 83.1%) as compared to the rest of the population (median, 53.8%; range, 27.5–73.7%) (Fig. 2).

None of the studied *ABCB1* genotypes was associated with interindividual differences in plasma pharmacokinetic parameters of paclitaxel (Table 1).

4. Discussion

The current data suggest a possible genetic predisposition to the occurrence of paclitaxel-induced neuropathy and neutropenia regulated by the *ABCB1* transporter gene. The finding that the patients who were homozygous wild-type for the *ABCB1* 3435C > T transition are less likely to develop clinically significant peripheral neuropathy indicates that ABCB1 may be differentially expressed in the blood–nerve barrier in a genotype-dependent manner. Likewise, the notion that patients carrying variants at both the *ABCB1* 2677G > T/A and 3435C > T loci have a significantly more pronounced relative decrease in their absolute neutrophil count at nadir is consistent with an inherited factor regulating ABCB1 expression in repopulating haematopoietic cells.

Interestingly, we found that the plasma pharmacokinetics of paclitaxel were not correlated with any of the evaluated

Table 1 – Association between ABCB1 genotype status and paclitaxel pharmacokinetics

Genotype	T > 0.05 μM (h)		AUCp ((ng/mL) × h)		AUCu ((ng/mL) × h)	
	Median (95% CI)	P	Median (95% CI)	P	Median (95% CI)	P
ABCB1 1236C > T						
Wild-type (N = 5)[a]	20.3 (8.8–34.2)	0.67	4657 (2909–9916)	0.34	507 (371–641)	0.39
Heterozygous (N = 17)	15.6 (9.3–19.3)[b]		5264 (3879–6235)		470 (445–519)	
Variant (N = 4)[a]	15.6 (8.8–24.9)		3547 (2309–5600)		407 (362–522)	
ABCB1 2677G > T						
Wild-type (N = 2)[a]	15.1 (8.8–21.3)	0.97	3348 (2909–3787)	0.18	540 (507–572)	0.26
Heterozygous (N = 13)	17.3 (9.6–20.7)[b]		5146 (3776–7762)		482 (371–641)	
Variant (N = 11)	12.6 (8.8–19.8)		4203 (2309–5600)		445 (362–516)	
ABCB1 3435C > T						
Wild-type (N = 4)[a]	9.7 (8.8–19.3)	0.23	4534 (2909–5146)	0.18	420 (313–572)	0.31
Heterozygous (N = 14)	19.8 (10.5–21.3)[b]		5485 (3787–6344)		512 (432–523)	
Variant (N = 8)	13.7 (8.7–18.9)		3656 (2259–5600)		448 (362–522)	

Abbreviations: T > 0.05 μM, duration of total plasma concentration of paclitaxel exceeding 0.05 μM; AUCp, area under the curve of total paclitaxel; AUCu, area under the curve of unbound paclitaxel; 95%CI, 95% confidence interval; P, Kruskal–Wallis test.
a Indicates that 95% confidence intervals are unavailable and the range is quoted instead.
b Indicates the genotype of the patient with unavailable T > 0.05 μM data.

ABCB1 SNPs, suggesting that a compensatory efflux mechanism, perhaps through ABCC2 (MRP2), may regulate paclitaxel elimination from the liver in patients with impaired ABCB1 function due to genetic variation. A more plausible explanation is the possibility that hepatocellular influx and subsequent metabolism of paclitaxel, rather than ABC transporter mediated biliary secretion, are the rate-limiting steps involved in systemic drug clearance.

The present data are in line with previous observations that the *ABCB1* 3435-T allele is associated with decreased expression of *ABCB1* in the liver, and decreased activity in CD56+ cells,[12] an effect that is likely due to decreased mRNA stability associated with this SNP.[13] Recent studies have indicated that the *ABCB1* 2677G > T/A allele may also independently contribute to altered *ABCB1* expression levels.[14] Overall, our data suggest that the *ABCB1* 3435C > T transition might have predictive power in the assessment of ABCB1 expression and activity at the blood–nerve barrier, whereas the 2677G > T/A and 3435C > T alleles combined are important contributing factors to the expression and activity of ABCB1 within repopulating neutrophils.

It should be noted that the small sample size of this study clearly warrants independent confirmation in a larger patient population. It is hoped therefore that the pharmacologic results presented here will encourage investigators to perform similar exploratory genotype approaches to gain insight into the mechanisms underlying interindividual pharmacodynamic variability of taxanes and other ABCB1 substrate drugs.

Conflicts of interest statement

The authors have no conflict of interest.

Disclaimer

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