Int J Clin Exp Med 2016;9(1):298-307
www.ijcem.com /ISSN:1940-5901/IJCEM0015721

Original Article

Influence of single nucleotide polymorphisms in *ABCB1*, *ABCG2* and *ABCC2* on clinical outcomes to paclitaxel-platinum chemotherapy in patients with non-small-cell lung cancer

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Received September 6, 2015; Accepted November 23, 2015; Epub January 15, 2016; Published January 30, 2016

Abstract: Platinum-based chemotherapy is the most common treatment for non-small cell lung cancer (NSCLC). Expression level of drug metabolism and transport genes are correlated with platinum-based chemotherapy efficiency which indicated that variants of genes from drug metabolism and transport pathway may have an influence on chemosensitivity. In this study, we assessed whether the presence of polymorphisms in *ABCB1, ABCC2* and *ABCG2* genes can affect the efficacy of paclitaxel-platinum treatment in NSCLC patients. 64 NSCLC patients who received plataxel and cisplatin/carboplatin chemotherapy were involved. *ABCB1* 1236T > C, *ABCB1* 3435C > T, *ABCC2* -24C > T, *ABCC2* 3972C > T, and *ABCG2* 421C > A were assessed for their association with the efficiency of paclitaxel-platinum chemotherapy. Among 5 polymorphisms assessed, *ABCG2* 421 A/A was associated with higher response rate (OR = 0.073; 95% CI: 0.009-0.602; P = 0.015) and *ABCC2* -24C > T was found to associate with progression-free survival (additive model: HR = 1.995; 95% CI: 1.171-3.398; P = 0.011). No association was observed between all these polymorphisms and overall survival. The results indicated that polymorphisms of the *ABCG2* and *ABCC2* genes might be predictive biomarkers of treatment efficiency for advanced NSCLC patients received paclitaxel-platinum treatment. This finding requires further validation.

Keywords: Non-small cell lung cancer, paclitaxel-platinum chemotherapy, single nucleotide polymorphism, *ABCB1*, *ABCC2*, *ABCG2*

Introduction

Lung cancer is the leading cause of cancer-related death in the world [1]. And non-small cell lung cancer (NSCLC) accounts for 80% of such deaths. The majority of patients present with stage III or IV disease. As operation is no longer suitable for advanced NSCLC patients, platinum -based therapy have become part of the mainstay chemotherapy treatment for them [2]. Paclitaxel promotes polymerization of tubulin dimers to form microtubules and stabilizes microtubules by preventing depolymerisation [3]. Paclitaxel combined platinum (cisplatin or carboplatin) therapy has been evaluated as one of the most common first-line treatments for non-small-cell lung cancer.

However, the 5-year survival rate remains less than 15% in advanced NSCLC patients [4]. The multidrug resistance (MDR) to chemotherapy is the main reason for the failure of chemotherapy in cancer patients. The adenosine triphosphate (ATP)-binding cassette (ABC) superfamily are the largest family of transmembrane proteins, which play an important role in the absorption, distribution and excretion of drugs, and also link to inter-individual differences in the efficacy and toxicity of many medications including toxic compounds and anticancer drugs, thereby influencing the sensitivity to chemotherapy [5, 6]. The ABC transporter superfamily includes medically important members such as multidrug resistance protein1 (MDR1; ABCB1; P-glycoprotein), multidrug resistance associat-

Table 1. Patient characteristics and clinical outcomes

Patient characteristic	Total	Number	%
Total patient	64		
Median age (range)	64	58 (38-73)	
Age	64		
≤ 58		32	50.0
> 58		32	50.0
Gender	64		
Male		44	68.8
Female		20	31.2
PS	64		
0-1		61	95.3
2		3	4.7
Smoking Status[a]	64		
Never smoker		31	48.4
Ever smoker		33	51.6
TNM Stage	64		
IIIA		3	4.7
IIIB		20	31.3
IV		41	64.0
Histological Type	64		
Adenocarcinoma		42	65.6
Squamous Cell		15	23.4
Adenosquamocarcinoma		2	3.1
Others		5	7.8
Response			
CR+PR	64	10	15.6
Median Time to outcomes (month)			
Progression-free survival (PFS)		52	8.6
Overall survival (OS)		50	18.6

Abbreviation: CR, complete response; ECOG PS, eastern cooperative oncology group performance status; PR, partial response; TNM, tumor-lymph node-metastasis. [a]Nonsmokers were defined as those who had smoked < 1 cigarette per day and for < 1 year in their lifetime.

ed protein 2 (MRP2; ABCC2) and the breast cancer resistance protein (BCRP; ABCG2), which are thought to be the most important transporters involved in drug transportation and absorption. Single nucleotide polymorphism (SNP) in the ABC transporters genes can influence the capacity or efficiency of these transporters. For a long time, *ABCB1, ABCC2* and *ABCG2* gene polymorphisms have been known to correlate with clinical outcomes of platinum-based chemotherapy for advanced NSCLC [7-11], which suggested that polymorphic variations in *ABCB1, ABCC2*, *ABCG2* may impact their expression and contribute to the therapeutic efficacy of chemotherapy.

By now, *ABCB1 (MDR1) 2677G > T/A* and *3435C/T* polymorphisms have been shown to be associated with the treatment response to docetaxel or vinorelbine-based chemotherapy in NSCLC patients [12, 13]. But similar studies about the association between ABC transporters gene polymorphisms with paclitaxel-platinum chemotherapy in lung cancer have been rarely reported. A vitro result suggests that high *ABCB1* mRNA expression may be a predictive biomarker for poor chemosensitivity to paclitaxel [14]. However, the role of ABC transporters gene polymorphisms in response to paclitaxel has not been fully explored in lung cancer. Nevertheless, these data let us hypothesize that differences in response to paclitaxel-based chemotherapy might be related to SNPs in genes encoding proteins which play a key role in ABC transporters superfamily. Therefore, in this study, we select polymorphisms of *ABCB1 (1236T > C, 3435C > T), ABCC2 (-24C > T, 3972C > T), and ABCG2 (421C > A)* to investigate if there is any relationship between these variants and response to paclitaxel-platinum combined chemotherapy in NSCLC patients.

Materials and methods

Patient recruitment

Eligible patients were aged 18 years or older, with histologically or cytologically confirmed inoperable stages III or IV NSCLC, and were given paclitaxel-platinum chemotherapy at Shanghai Chest Hospital in Shanghai, China, and were required to fulfill the following criteria: the presence of a measurable lesion; Eastern Cooperative Oncology Group performance status (ECOG PS) 0~2; an absolute neutrophil count (ANC) ≥ 1.5×10^9 cells/L; platelet count ≥ 100×10^9 cells/L; serum creatinine ≤ 1.5* upper limit normal; aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 1.5* upper limit normal; estimated creatinine clearance ≥ 60 mL/min. Patients with symp-

Table 2. Association between Polymorphisms and response

SNP	Genetic Model[a]	Genotype	Number/ Total[b]	%	Fisher's exact test	Logistic regression analysis[d]		
					P[c]	OR	95% CI	P
ABCB1 3435C > T		C C	2/22	9.1	0.458	1 (Reference)		
		T C	4/29	13.8		1.275	0.154-10.532	0.822
		T T	3/12	25.0		0.457	0.051-4.092	0.484
	Add					0.633	0.199-2.017	0.439
ABCB1 1236T > C		T T	4/30	13.3	0.777	1 (Reference)		
		C T	5/29	17.2		0.931	0.178-4.877	0.932
		C C	1/5	20.0		0.149	0.010-2.327	0.175
	Add					0.568	0.158-2.035	0.385
ABCC2 3972C > T		G G	6/37	16.2	0.336	1 (Reference)		
		A G	2/20	10.0		1.947	0.264-14.363	0.513
		A A	2/6	33.3		0.119	0.011-1.294	0.080
	Add					0.541	0.169-1.737	0.302
ABCC2 -24C > T		G G	8/38	21.1	0.240	1 (Reference)		
		A G	1/21	4.8		7.458	0.600-92.650	0.118
		A A	1/4	25.0		0.158	0.010-2.559	0.194
	Add					1.404	0.313-6.291	0.657
ABCG2 421C > A		C C	3/34	8.8	**0.003****	1 (Reference)		
		A C	2/21	9.5		0.692	0.095-5.049	0.716
		A A	5/8	62.5		0.073	0.009-0.602	**0.015***
	Add					0.290	0.097-0.861	**0.026***

Abbreviation: CI, confidence interval; OR, odds ratio. [a]Additive genetic model was used. Add is short for Additive model. [b]Numbers represent the patients who response to chemotherapy in the same genotype group. [c]*P* < 0.05 was shown in bold. [d]Multiple logistic regression analysis adjusted for covariate was used. Covariate for response was TNM stage. *P* < 0.05 was shown in bold. *P<0.05, **P<0.01.

tomatic brain metastases, spinal cord compression and uncontrolled massive pleural effusion were excluded. Other eligibility criteria were: absence of active infection, history of significant cardiac disease (unstable angina, congestive heart failure, myocardial infarction within the previous 6 months, ventricular arrhythmias) or malnutrition (loss of ≥ 20% of the original body weight). The study was approved by the ethics committees of Shanghai Chest Hospital. All patients gave consent to participate in the study. In total, 64 patients with advanced (III or IV) NSCLC were included. All of the 64 patients were Han Chinese.

All the patients enrolled in this study received the first-line paclitaxel-platinum chemotherapy. Paclitaxel (175 mg/m^2) plus cisplatin (75 mg/m^2) or carboplatin (AUC = 5) on day 1, repeated every 3 weeks. All chemotherapy drugs were administered intravenously, and all treatments were for two to six cycles unless the patient met the criteria for progressive disease (PD) or experienced unacceptable toxicity. Patient responses to the treatment were evaluated after first cycle of chemotherapy by the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines version 1.0 [15]. Survival data were collected by follow-up calls and clinical medical records.

SNP genotyping

Five milliliter blood samples were collected from each patient and frozen (-80°C) until it was assayed. The genomic DNA was extracted using QIAamp DNA Maxi kit (Qiagen GmbH). Patients' genotypes of *ABCB1* (*1236T > C*, *3435C > T*), *ABCC2* (*-24C > T, 3972C > T*), and *ABCG2* (*421C > A*) were determined by the Sequenom MassARRAY iPLEX platform using the matrix-assisted laser desorption/ionization time-of-flight mass spectrometer.

Statistical analysis

Statistical analysis was performed using SPSS software package Version 13.0 (SPSS Inc., Chicago, USA). Pearson X^2 test or log-rank test

Table 3. Association between SNP and progression free survival

SNP	Genetic Model[a]	Genotype	MST	Log-rank	Cox proportional hazards regression[c]		
				P[b]	HR	95% CI	P
ABCB1 3435C > T		C C	6.0	0.430	1 (Reference)		
		T C	12.3		0.638	0.305-1.335	0.233
		T T	9.4		0.646	0.259-1.610	0.348
	Add				0.775	0.484-1.241	0.289
ABCB1 1236C > T		T T	8.6	0.886	1 (Reference)		
		C T	9.4		1.129	0.570-2.238	0.727
		C C	8.6		1.276	0.425-3.829	0.663
	Add				1.130	0.692-1.843	0.625
ABCC2 3972C > T		G G	9.4	0.503	1 (Reference)		
		A G	9.9		1.416	0.702-2.854	0.331
		A A	8.0		1.663	0.550-5.024	0.368
	Add				1.329	0.819-2.156	0.250
ABCC2 -24C > T		G G	13.2	**0.032***	1 (Reference)		
		A G	4.8		2.072	1.048-4.182	**0.042***
		A A	4.7		3.766	1.048-13.533	**0.042***
	Add				1.995	1.171-3.398	**0.011***
ABCG2 421C > A		C C	6.9	0.416	1 (Reference)		
		A C	13.2		0.611	0.292-1.280	0.192
		A A	12.3		0.835	0.311-2.243	0.720
	Add				0.811	0.496-1.326	0.404

Abbreviation: CI, confidence interval; HR, hazard ratio; MST, median survival time. [a]Additive genetic model was used. Add is short for Additive model. [b]*P* < 0.05 was shown in bold. [c]Multiple Cox proportional hazards regression analysis adjusted for covariate was used. Covariates for PFS were histologic type of disease and gender. *P* < 0.05 was shown in bold. *P<0.05.

was used to test the demographic and clinical characteristics against clinical outcomes, depending on which variables were considered. Characteristics which had a *P*-value < 0.1 were regarded as covariates. The significance of differences in genotypes between good and poor responders was calculated by Fisher's exact test. Logistic regression was used to verify the relationship between chemosensitivity and genetic polymorphisms with an odds ratio (OR) and 95% confidence interval (CI), adjusted for covariates mentioned above. The association between genotypes and survival including overall survival (OS) and progression-free survival (PFS) was tested by Cox proportional hazards regression model with hazard ratio (HR) and 95% confidence interval (CI). Patients who had complete response (CR) or partial response (PR) were regarded as good responders, and those who had stable disease (SD) and progressive disease (PD) were grouped as poor responders. Overall survival (OS) was calculated from the date of first cycle chemotherapy to the date of last follow-up or death. Progression free survival (PFS) was calculated from the date of first cycle chemotherapy to the date of disease progression to the last follow-up. Patients who were not deceased were censored at the last date they were known to be alive based on the date of last contact. All *P* values reported were two-sided, and *P* < 0.05 was considered statistically significant.

Results

Patient characteristics

64 patients with Stage III or IV NSCLC confirmed cytologically or histologically were enrolled in this study. Patient characteristics are shown in **Table 1**. 4.7% had stage IIIA disease, 31.2% had Stage IIIB disease and 60.9% had stage IV disease. Median age was 58 years (range 38-73), 66.8% were male and 65.6% had adenocarcinoma. There were 33 never smokers (51.6%). No patient had received thoracic radiotherapy. Some patients were excluded for survival analysis because of loss to follow-up.

Table 4. Association between SNP and overall survival

SNP	Genetic Model[a]	Genotype	MST	Log-rank	Cox proportional hazards regression[c]		
				P[b]	HR	95% CI	*P*
ABCB1 3435C > T		C C	20.6	0.770	1 (Reference)		
		T C	18.8		1.272	0.633-2.558	0.499
		T T	15.5		1.454	0.609-3.472	0.400
	Add				1.213	0.793-1.855	0.373
ABCB1 1236C > T		T T	15.5	0.698	1 (Reference)		
		C T	18.8		1.091	0.569-2.090	0.794
		C C	21.1		0.656	0.220-1.953	0.448
	Add				0.902	0.585-1.389	0.639
ABCC2 3972C > T		G G	24.8	0.729	1 (Reference)		
		A G	16.5		1.284	0.686-2.404	0.435
		A A	18.8		0.683	0.224-2.078	0.502
	Add				0.973	0.663-1.495	0.902
ABCC2 -24C > T		G G	21.1	0.401	1 (Reference)		
		A G	15.5		1.357	0.730-2.522	0.334
		A A	18.8		0.341	0.077-1.514	0.157
	Add				0.882	0.565-1.377	0.581
ABCG2 421C > A		C C	18.2	0.454	1 (Reference)		
		A C	21.1		1.112	0.583-2.118	0.748
		A A	15.0		1.317	0.456-3.801	0.611
	Add				1.134	0.716-1.795	0.592

Abbreviation: CI, confidence interval; HR, hazard ratio; MST, median survival time. [a]Additive genetic model was used. Add is short for Additive model. [b]*P* < 0.05 was shown in bold. [c]Multiple Cox proportional hazards regression analysis adjusted for covariate was used. Covariates for OS were histologic type of disease and gender. *P* < 0.05 was shown in bold.

Association between polymorphisms and response

Table 2 shows the association of polymorphisms with treatment response in patients receiving paclitaxel-platinum chemotherapy. The response rate of patients with *ABCG2 421 A/A* genotype was 62.5%, which was numerically higher than patients with C/C genotype (8.8%). Logistic regression analysis adjusted for TNM Stage showed that *ABCG2 421C > A* played a protective role in paclitaxel-platinum treatment (*P* = 0.026, OR = 0.290, 95% CI: 0.097-0.861). However, *ABCB1 3435C > T*, *ABCB1 1236T > C*, *ABCC2 3972C > T* and *ABCG2 -24C > T* were not significantly different between patients who responded and that did not respond to the paclitaxel-platinum treatment.

Association between polymorphisms and survival

Results of survival analysis are shown in **Tables 3** and **4**. Histologic type of disease was significantly associated with overall survival (*P* = 0.007), and gender also has a marginal effect on overall survival (*P* = 0.077) (data not shown). No demographic or clinical characteristics were associated with PFS (data not shown). Thus histologic types and gender were regarded as covariates which were adjusted in Cox proportional hazards regression model for OS analysis. Among all the 5 SNPs assessed, *ABCC2* (*-24C > T*) exhibited significant association with PFS (**Table 3**). Patients carrying AA genotype had a much shorter PFS (median survival time: 4.7 months) compared to those having GG genotype (median survival time: 13.2 months). Additive model demonstrated that A variant of *ABCC2* (*-24C > T*) was a risk factor in PFS (HR = 1.995, 95% CI: 1.17-3.40; *P* = 0.011) of paclitaxel-platinum treatment. For *ABCB1 3435C > T*, *ABCB1 1236T > C*, *ABCC2 3972C > T* and *ABCG2 421C > A*, however, no significant difference in PFS or OS was observed.

Discussion

Clinically, NSCLC shows remarkable inter-individual variability in response to paclitaxel-plati-

num combination chemotherapy. Multidrug resistance (MDR) mediated by a number of proteins in the ABC transporter family remains a major obstacle to successful treatment of lung cancer. Among the ABC proteins, some members including *ABCB1*, *ABCC2* and *ABCG2* are expressed in many human tumors, which indicated that they were likely to contribute to multidrug resistance of cancer chemotherapy. The inter-individual variations in activity and expression levels of *ABCB1 (MDR1)*, *ABCC2 (MRP2)* and *ABCG2 (BCRP)* might have effect on drug absorption and elimination. Single nucleotide polymorphisms in ABC transporters may play a role in response to drug therapy and chemosensitivity. In this study, we analyzed the associations between 5 SNPs located on the *ABCB1*, *ABCC2* and *ABCG2* genes, with clinical outcomes of paclitaxel-platinum treated NSCLC patients. We demonstrated that the genotypes of *ABCG2 421C > A* had a significant association with response to paclitaxel-platinum, and *ABCC2 -24C > T* played a vital role in prolonged PFS.

ABCB1

The human multidrug-resistance *(MDR)-1* gene which also known as *ABCB1*, encodes P-glycoprotein (PGP) which functions as an energy-dependent drug efflux pumps for a wide range of compounds including cytotoxic drugs such as Vinca alkaloids, taxanes, anthracyclines and topoisomerase inhibitors [16-18].

ABCB1 gene polymorphisms may have an impact on the expression and function of P-gp, thereby influencing the response to chemotherapy [19-23]. Previously, great attention was brought to the *ABCB1 3435C > T* because of its suppressive effect on ABCB1 protein expression and function [24]. Numerous studies have investigated the association between *ABCB1 3435C > T* and clinical response or survival. Pan et al. reported that the *ABCB1 3435 CC* genotype was associated with a better response in NSCLC patients treated with vinorelbine-cisplatin chemotherapy ($P = 0.025$) [13]. Sohn et al. found the *3435 CC* genotype was associated with a significantly better chemotherapy response compared with the combined *3435 CT* and *TT* genotype in small cell lung cancer (SCLC) patients who received a combination chemotherapy of etoposide-cisplatin [25]. On the other hand, Isla et al. did not find any effect of the *ABCB1 3435C > T* on the outcome of docetaxel-cisplatin treatment of patients with non-small cell lung cancer [26]. While Pan et al. found that the 3435 CC genotype was associated with a better response to chemotherapy compared with the combined 3435 CT and TT genotypes although the difference was not statistically significant ($P = 0.123$) [12]. In ovarian cancer, a high expression of P-glycoprotein in tumor cells has been shown to correlate with a poor response to paclitaxel treatment [27, 28], and *ABCB1* polymorphisms were also found to be associated with resistance to paclitaxel treatment [29].

However, none of *ABCB1* gene SNPs examined in this study had any association with response to paclitaxel-platinum chemotherapy, OS or PFS. It might be because the limited number of SNPs selected for this study missed important functional variants of *MDR1*. Limited sample size may be considered as another influencing factor. Further investigation is required to illustrate the role of *ABCB1* in clinical outcomes of NSCLC.

ABCC2

Multidrug resistance-associated protein 2 (MRP2), which is also called ABCC2, is expressed in the outer plasma membrane as well as in intracellular vesicles and the Golgi apparatus. ABCC2 expresses in many tumor tissues, and the tumor cells overexpressing ABCC2 might result in multidrug resistance [30]. ABCC2 has been reported to involve in exporting anticancer drug [31], including cisplatin, doxorubicin, etoposide and methotrexate [32, 33]. To date, few studies have addressed the impact of *ABCC2* polymorphisms on chemotherapy efficacy. Campa et al. found that *ABCC2 -24C > T* was moderately associated with a poor response to chemotherapy but strongly with shorter progression-free survival and overall survival in SCLC but not NSCLC patients [34]. Han et al. found *ABCC2 -24TT* genotype was associated with higher response rates ($P = 0.031$) and longer progression-free survival ($P = 0.035$) in advanced NSCLC patients treated with irinotecan and cisplatin chemotherapy [10]. Sun et al. observed the *ABCC2 -24 CC* genotype significantly decreased platinum-based chemotherapy response ($P = 0.002$), suggesting that the polymorphic status

of *ABCC2 -24C > T* might predict treatment response of advanced stage NSCLC patients [8].

Although no association was observed between *ABCC2 -24C > T* and response to paclitaxel-platinum chemotherapy, *ABCC2 -24C > T* demonstrated significant association with PFS in this study, which was in accordance with previous studies mentioned above. The results suggested that variants of *ABCC2* are probably important determinants in cellular response to paclitaxel-based chemotherapy, which might be predictive markers of response to paclitaxel-platinum treatment in advanced NSCLC.

ABCG2

ABCG2 which associated with lower BCRP protein expression [35] caused by platinum agents, paclitaxel, methotrexate and topotecan that mediates drug absorption, distribution and elimination, appears to be associated with clinical outcomes of chemotherapy [36-46]. Among single nucleotide polymorphisms in *ABCG2* gene, *ABCG2 421C > A* is the most common mutant allele in Asians (~30%) [47]. A positive association between *ABCG2 421C > A* polymorphisms and cancer has been reported in two studies. Tian et al. reported the *421C > A* variant (CA+AA versus CC) in *ABCG2* was associated with a longer median PFS (22.7 versus 16.8 months, $P = 0.041$) and similar OS (HR = 0.88, 95% CI = 0.67-1.15, $P = 0.356$) among women with advanced stage ovarian cancer treated with platinum and taxane-based chemotherapy [48]. Zhai et al. showed that the *ABCG2 421C > A* C/A and C/C genotypes were significantly associated with low levels of pretreatment WBC counts, which are a prognostic indicator in pediatric patients with acute lymphoblastic leukemia [49].

In this article, data suggested that *ABCG2* was associated with neither overall survival nor progression-free survival. However, the *ABCG2 421* A/A genotype was significantly associated with higher response rate ($P = 0.015$). The better response rate might be due to a reduced efflux of paclitaxel from the tumor cells or a reduced elimination from the body which giving higher plasma concentrations.

Conclusion

To our knowledge, this is the first study demonstrating that the *ABCG2 421C > A* polymorphism is associated with response in advanced NSCLC patients treated with platinum-based chemotherapy. The most important limitation of this study was the small sample size. To confirm the results observed in the present study, further larger sample validation was needed in an independent data set.

Our finding suggests that polymorphisms in *ABCG2* and *ABCC2* might be potential biomarkers which can be used to predict clinical outcome and improve prognosis in NSCLC patients treated with paclitaxel-based combination chemotherapy, although larger sample size studies and *in vivo* functional studies are required to confirm the results and identify the potential biological basis of these findings.

Acknowledgements

This work was supported by Shanghai Science and Technology Research Program (06DZ19501). We thank Dr. Jing Wu for help with sample collection. We also thank our volunteers for donating their blood and collaborators for collection of blood sample and information.

Disclosure of conflict of interest

None.

Abbreviations

CI, confidence interval; HR, hazard ratio; MDR, multidrug resistance; NSCLC, Non-small cell lung cancer; OR, odds ratio; OS, overall survival; PFS, progression-free survival; SNP, single nucleotide polymorphism.

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