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ORIGINAL RESEARCH

The Association Between Genetic Polymorphisms of Transporter Genes and Prognosis of Platinum-Based Chemotherapy in Lung Cancer Patients

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Objective: Platinum-based chemotherapy is the first-line treatment of lung cancer. However, different individual and genetic variation effect therapy for lung cancer. The purpose of this study was to evaluate the association between transport genes genetic polymorphisms and the prognosis of platinum-based chemotherapy in lung cancer patients.

Methods: A series of 593 patients with treatment of platinum-based chemotherapy were recruited for this study. A total of 21 single-nucleotide polymorphisms in nine transporter genes were selected to investigate their associations with platinum-based chemotherapy prognosis.

Results: Patients with ABCG2 rs1448784 CC genotype had a significantly shorter PFS than CT or TT genotypes (Additive model: HR = 1.54, 95% CI = 1.02–2.35, $P = 0.040$). In stratification analysis, SLC22A2 rs316003, SLC2A1 rs4658 were related to PFS and AQP9 rs1867380, SLC2A1 rs3820589, SLC22A2 rs316003 indicated were related to OS of platinum-based chemotherapy prognosis.

Conclusion: Genetic polymorphisms of rs1448784 in ABCG2 might be potential clinical marker for predicting the prognosis of lung cancer patients treated with platinum-based chemotherapy.

Keywords: lung cancer, platinum-based chemotherapy, prognosis, transporter gene, single nucleotide polymorphisms, SNPs

Introduction

Lung cancer is the most frequent cause of cancer-related deaths worldwide.[1] Every year, 1.8 million people are diagnosed with lung cancer, and 1.6 million people die as a result of the disease.[2,3] Lung cancer is divided into two broad histologic classes: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). NSCLC consists of adenocarcinoma, squamous cell cancer and large cell lung cancer, nearly 90% of lung cancers are NSCLC. Current, treatment options for lung cancer include surgery, radiation therapy, chemotherapy, and targeted therapy.[4] Among of them, platinum-based chemotherapy is still the first-line chemotherapy regimens.[5] Although clinical diagnosis and treatment improvement, the prognosis for patients with lung cancer is still unsatisfactory.

The drug resistance involved in mechanism in cells, including enhanced cisplatin-resistant (DDP) cell detoxification, inhibition of apoptosis, and enhanced DNA repair capabilities.[6,7] Genetic polymorphisms are also an important factor affecting the prognosis of chemotherapy and can explain the interindividual difference.[8,9] Therefore, an understanding of different individual and potential genetic variation that might contribute to more effective therapy effect varies for lung cancer.[10]

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Platinum is mainly eliminated by the proximal tubules in the kidney, and transporters expressed in the kidney play important roles in the distribution and excretion of platinum.[11,12] There are studies have found that several transporters lead to mediate resistance to platinum compounds in the cancer cells.[13,14] Solute carrier (SLC) and ATP-binding cassette (ABC) transporters have key roles in interorgan and interorganism small-molecule communication, together with the neuroendocrine, growth factor-cytokine, and other homeostatic systems, regulate local and whole-body homeostasis.[15] Susceptibility to cisplatin is taken up into the renal proximal tubular cells mainly via SLC22A2 organic cation transporter 2 (OCT2) and secreted into lumen via other transporters including SLC47A1 multidrug and toxin extrusion 1 (MATE1).[16,17]

The ATP-binding cassette (ABC) transporters as efflux transporters, are responsible for moving drugs out of cells. ABC superfamily categorized into seven subfamilies (A to G), which have been identified related to multidrug resistance (MDR) development.[18–20] ABCC2 polymorphism were association with survival ovarian and lung cancer patients following chemotherapy treatment.[21,22] ABCG2 has been implication upregulation transport affected to be more resistance to chemotherapy.[23,24]

Aquaporins (AQPs) are members of a family of transmembrane proteins, which mainly mediated water transmembrane exchange.[25] Studies have suggested that overexpression of AQP1 was involved in poor prognosis for colon cancer.[26] AQP9 can also activate RAS signal and sensitize tumor cells to chemotherapy drugs in colorectal cancer.[27] Previous studies indicated that AQP9 rs1516400 and AQP2 rs7314734 showed significant related to chemotherapy response.[28] The expression of AQP2 and AQP9 were reduced in platinum resistant lines presenting that they are the potential new platinum drug transporters.[29]

This study aimed to investigate the association of a large numbers of transport polymorphisms with prognosis of platinum-based chemotherapy in lung cancer patients.

Materials and Methods

Study Subjects

This prospective study was conducted to investigate the association of transport polymorphisms with the prognosis of lung cancer. Totally 593 lung cancer patients were enrolled from the Affiliated Cancer Hospital or Xiangya Hospital of Central South University (Changsha, Hunan, China) from August 2009 to January 2013. All patients were selected by the following inclusion criteria: (1) lung cancer were assessed based on histologically or cytologically examination, and primary tumor in the lung; (2) Patients should have been exposed to platinum-based chemotherapy at least 2 periods; (3) Patients who had never received any radical or biological therapy before chemotherapy. Written informed consent obtained from all subjects. The study was approved by the Ethics Committee of Xiangya School of Medicine, Central South University.

Selection of Genes and Polymorphisms

All of the common genetic variants in ABCB1, ABCB10, ABCB11, ABCC2, ABCG2, SLC22A2, SLC47A1, SLC2A1, AQP1, AQP2 and AQP9 were selected by Haploview (Broad Institute, Cambridge, MA, USA) using pair-wise tagging with default settings (pairwise r^2 threshold = 0.8). SNPs with a minor allele frequency (MAF) ≥5% were selected. Finally, twenty-one SNPs were genotyped in the patients (Table 1).

DNA Extraction and Genotyping

Genomic DNA was extracted from 5 mL peripheral blood using the FlexiGene DNA Kit according to the manufacturer's instruction (Qiagen, Hilden, Germany) and stored at −20°C until use. The 21 genetic polymorphisms of genes involved in transport were selected for genotyping based on a previous study.[30] The candidate genetic polymorphisms were genotyped using the MassARRAY system (Sequenom, San Diego, CA, USA).

Statistical Analysis

All of the statistical analysis were performed using PLINK (ver 1.07, http://pngu.mgh.harvard.edu/purcell/plink/) and SPSS 20.0 (SPSS Inc, Chicago, Illinois, USA). The associations of genetic polymorphisms with overall survival (OS)

Table 1 The 21 Single Nucleotide Polymorphisms Examined in This Study

Gene	SNPs	Alleles	Call Rates (%)	MAF
ABCC2	rs3740066	C/GT	96.54	0.29
	rs2273697	G/A	99.51	0.19
	rs717620	C/T	95.56	0.13
ABCG2	rs2231142	G/CT	98.02	0.12
	rs1448784	A/G	98.55	0.07
ABCB1	rs3213619	A/G	99.51	0.06
	rs17064	T/A	98.84	0.06
ABCB11	rs495714	C/AGT	98.55	0.49
SLC22A2	rs316003	C/AT	96.05	0.31
	rs316019	A/C	96.30	0.14
SLC2A1	rs1385129	G/AC	97.11	0.24
	rs3806400	C/AT	99.13	0.13
	rs4658	C/GT	99.42	0.38
	rs3820589	A/T	99.71	0.10
SLC47A1	rs2289669	G/A	95.80	0.36
AQP2	rs10875989	T/ACG	98.84	0.48
	rs296766	T/AC	100	0.11
	rs3759126	A/CG	99.13	0.28
AQP9	rs1516400	G/ACT	98.27	0.48
	rs1554203	A/CG	99.71	0.10
	rs1867380	A/CGT	99.13	0.16

Abbreviation: MAF, minor allele frequency.

and progression-free survival (PFS) were evaluated with hazard ratios (HRs) using PLINK analysis. The Log rank test was used to examine the difference in OS or PFS between groups. Kaplan–Meier plot was used to visualize the results. Cox proportional hazard models were analyzed to select the covariates, and there was no clinical factors significantly related to PFS/OS (Table 2). Three genetic models (Additive model: compares major allele homozygotes versus heterozygotes versus minor allele homozygotes. Dominant model: major allele homozygous verses combined heterozygotes and minor allele homozygous groups. Recessive model: comparing major allele-carrying genotypes with homozygous variant genotype.) were constructed to evaluate the association between SNPs and prognosis of lung cancer patients. All the P-values were two-sided, $P < 0.05$ were supposed to be significant.

Results

Baseline Characteristics of the Lung Cancer Patients

A total of 593 lung cancer patients met our entry criteria in this study. The clinicopathological characteristics of the patients are given in Table 2. The median survival of overall survival (MST-OS) is 4.04 year and progression free survival (MST-PFS) is 3.49 year. The median age of the patients was 56 years old (range from 21 to 77). A total of 468 (78.9%) patients were male, and 366 (61.7%) patients were smokers. The histopathological types of tumors included NSCLC which consisted of squamous cell carcinoma (n = 197, 33.2%), adenocarcinoma (n = 236, 39.8%) and others (n = 22, 3.7%), SCLC (n = 122, 20.6%). For clinical stage, most patients (87.5%) were advance stage (III/IV/ED). We examined the association between clinical factors and PFS/OS, but no clinical factors remained significant. The detail clinical in lung cancer patients is summarized in Table 2.

Association of Polymorphisms with Lung Cancer Prognosis

We used PLINK to analyze these transporter gene of genetic polymorphism on lung cancer patient of progression free survival (PFS) and overall survival (OS). The results showed that genetic polymorphism of ABCG2 rs1448784 was

Table 2 Main Clinical Characteristics of Lung Cancer Patients and Prognosis Analysis

Characteristics	Patients N(%)	Death N(%)	MST-OS (Year)	P	MST-PFS (Year)	P
Total	593	416	4.04		3.49	
Age(years)						
≤60	412(69.4)	280(67.3)	4.38	0.822	3.43	0.692
>60	181(30.5)	136(32.6)	4.65		3.75	
Gender						
Male	468(78.9)	335(80.5)	4.38	0.082	3.45	0.449
Female	123(20.7)	80(19.2)	4.53		3.43	
Smoking status						
Non-smoker	224(37.8)	149(35.8)	4.53	0.134	3.28	0.411
Smoker	366(61.7)	265(63.7)	4.36		3.45	
Family history of cancer						
No	380(64.1)	275(66.1)	4.27	0.521	3.06	0.580
Yes	22(3.7)	17(4.1)	3.77		3.67	
Histology						
NSCLC				0.361		0.093
LUSC	197(33.2)	134(32.2)	4.096		3.449	
LUAD	236(39.8)	176(42.3)	4.496		5.001	
Others	22(3.7)	14(3.2)	4.469		3.946	
SCLC	122(20.6)	92(22.1)	4.319		4.268	
Stage						
I/II/LD	68(11.5)	44(10.6)	4.62	0.345	4.30	0.558
III/IV/ED	519(87.5)	363(87.3)	4.31		3.41	

Abbreviations: NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; LUSC, squamous cell carcinoma; LUAD, adenocarcinoma.

significantly associated with the PFS of lung cancer patients in additive model (HR = 1.54, 95% CI = 1.02–2.35, P = 0.040) (Table 3, Figure 1). Patients who carry the ABCG2 rs1448784 CC genotype had a significantly shorter MST-PFS than the patients who had CT or TT variant genotypes (MST-OS: 2.871, 3.800, 3.249 years, respectively). It suggested that there was a significant associated between the C allele of rs1448784 increased prognosis risk of lung cancer.

Stratification Analyses of Association Between Polymorphisms and Prognosis

Stratification analyses were used to explore the association of the SNPs with PFS and OS in the subgroup analysis by age, gender, smoking status, family history, histology and clinical stage. For consideration of ABCG2 rs1448784 was associated with PFS of platinum-based chemotherapy prognosis, we conducted stratification analysis of rs1448784 firstly. As shown in Figure 2, the polymorphisms of ABCG2 rs1448784 was correlated to progression free survival in male patients in additive (HR = 1.92, 95% CI = 1.16–3.17, P = 0.011) and dominant models (HR = 2.06, 95% CI = 1.13–3.76, P = 0.019), smoking patients in additive model (HR = 1.96, 95% CI = 1.10–3.50, P = 0.024), SCLC patients in additive model (HR = 2.62, 95% CI = 1.20–5.75, P = 0.027) and dominant model (HR = 3.24, 95% CI = 1.25–8.37, P = 0.021).

Table 3 Association of the ABCG2 rs1448784 Polymorphisms and PFS in Lung Cancer Patients

Gene	Polymorphisms	Genotypes	MST	Additive		Dominant		Recessive	
			(Year)	OR (95%CI)	p	OR (95%CI)	p	OR (95%CI)	p
ABCG2	rs1448784	CC CT TT	2.871 3.800 3.249	1.54(1.02–2.35)	**0.040***	1.54(0.88–2.53)	0.133	3.33(0.99–11.17)	0.051

Notes: Additive model: comparison between minor allele subjects and major allele subjects. Dominant model: comparison between minor allele carriers and major homozygous subjects. Recessive model: comparison between major allele carriers and minor homozygous subjects. p< 0.05 are indicated in bold text; *p< 0.05.
Abbreviation: MST, median survival time.

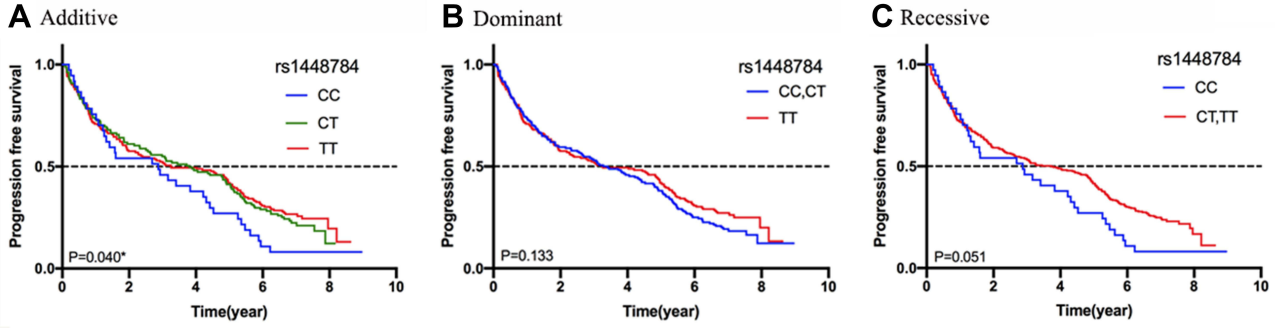

Figure 1 The ABCG2 rs1448784 is significantly associated with PFS in lung cancer patients treated with platinum-based chemotherapy. (**A**) PFS of lung cancer patients by rs1448784 using additive model. (**B**) PFS of lung cancer patients by rs1448784 using dominant model. (**C**) PFS of lung cancer patients by rs1448784 using recessive model.

We also conducted stratified analyses of the other SNPs. The results indicated that there were significant associated between the SLC22A2 rs316003, SLC2A1 rs4658 and PFS in smoking patients (additive model: HR = 1.98, 95% CI = 1.04–3.76, $P = 0.036$; HR = 0.61, 95% CI = 0.38–0.99, $P = 0.044$, respectively) (Table 4).

For OS analyses, AQP9 rs1867380 was significant related to OS in subgroup of patients without family history (recessive model: HR = 0.15, 95% CI = 0.02–0.89, $P = 0.037$), LUAD (additive model: HR = 0.24, 95% CI = 0.06–0.99, $P = 0.049$) and advance stage (III/IV/ED) patients (recessive model: HR = 0.17, 95% CI = 0.03–0.99, $P = 0.049$) subgroups. For SLC2A1 rs3820589, patients without family history were related to better OS (dominant model: HR = 0.30, 95% CI = 0.10–0.97, $P = 0.043$). For SLC22A2 rs316003, patients with LUSC histological type (additive model: HR = 12.43, 95% CI = 1.62–94.27, $P = 0.015$; dominant model: HR = 13.77, 95% CI = 1.76–107.7, $P = 0.012$) and smoking status (additive model: HR = 3.88, 95% CI = 1.15–13.07, $P = 0.029$; dominant model: HR = 4.13, 95% CI = 1.16–14.78, $P = 0.029$) were related to OS (Table 4).

Discussion

We evaluated association between 21 genetic polymorphisms of transport genes (ABC family, AQP family, SLC47A1 and SLC2A1) and prognosis of lung cancer patients treated with platinum-based chemotherapy. In terms of PFS, rs1448784 in ABCG2 were significantly related to prognosis of lung cancer patients with received platinum-based chemotherapy. In detail, rs1448784 who carry CC genotype in lung cancer patients received platinum-chemotherapy had worse PFS compared with carrying CT and TT genotypes.

Our results showed that ABCG2 rs1448784 were significantly associated with PFS in different subgroups. Male patients, smoking patient or those diagnosed with SCLC who carrying CC genotype had shorter PFS ($P = 0.011$, 0.024, 0.027, respectively) than patients carrying TT. Male and SCLC patients carrying TT or CT genotypes had longer PFS than carrying CC genotype ($P = 0.019$, 0.021, respectively).

SLC22A2, a gene which product is the organic cation transporter OCT2 responsible for cellular cisplatin uptake in renal proximal tubule cells,[31,32] affected the severity of tubular injury process due to cisplatin accumulation. Allele A at SLC22A2 rs316019 was associated with increased risk, while genotype AC was associated with a higher risk of cisplatin nephrotoxicity.[11] Our results demonstrated that SLC22A2 rs316003 was associated with PFS of lung cancer received platinum-based chemotherapy. Patients with smoking status, carried T allele of the rs316003 polymorphism had better PFS than carried C allele. Furthermore, smoking patients carrying TT or/and CT genotypes had better OS than CC genotype.

SLC2A1 is a member of solute carrier family 2, and it encodes the glucose transporter 1 (GLUT1) glucose transporter.[33] Previous studied have indicated that rs4658 was related to lung cancer chemotherapy toxicity.[34,35] Our results also demonstrated that smoking patients carrying GG genotype had longer PFS comparing to CC genotype. For SLC2A1 rs3820589, patients with family history who carrying TT and TA genotype had longer OS than AA genotype.

AQP9, as an aquaglyceroporin, is expressed in many cells and plays important role in tumor initiation and progression.[36,37] Previous studies AQP9 affected RAS/PI3K/AKT/ERK signaling pathway to regulate the expression of GSK3β and p21,

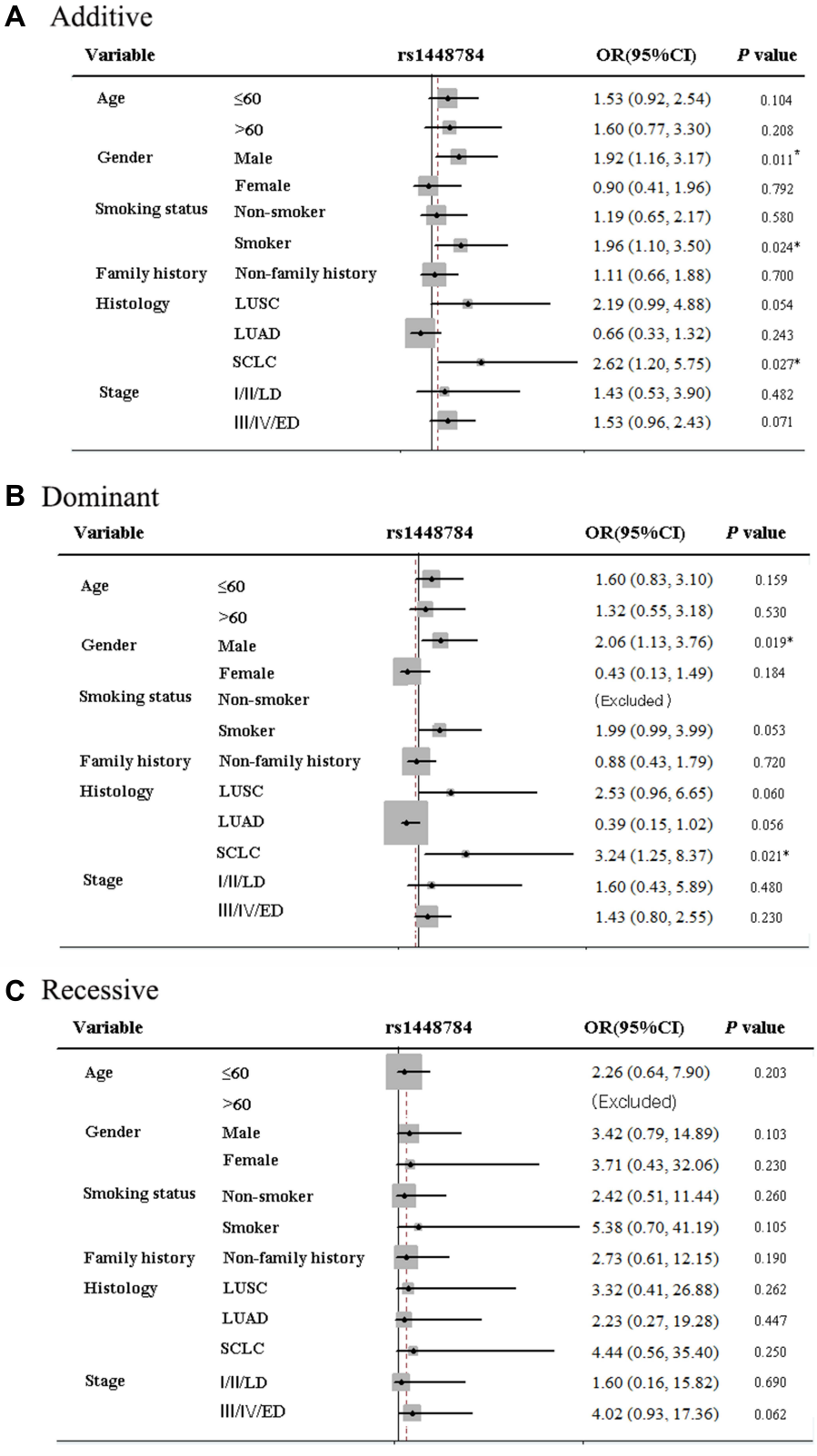

Figure 2 Stratification analysis of the associations of ABCG2 rs1448784 polymorphisms with PFS in lung cancer patients. (**A**) ABCG2 rs1448784 polymorphisms is significantly association with the PFS in additive model. (**B**) ABCG2 rs1448784 polymorphisms is significantly association with the PFS in dominant model. (**C**) ABCG2 rs1448784 polymorphisms is significantly association with the PFS in recessive model.

Table 4 Stratification Analyses of Association Between Polymorphisms and PFS or OS in Lung Cancer Patients

PFS/OS	Gene	Polymorphisms	Subgroup	Additive		Dominant		Recessive	
				OR (95%CI)	p	OR (95%CI)	p	OR (95%CI)	p
PFS	SLC22A2	rs316003	Smoker	1.98(1.04–3.76)	**0.036**	1.89(0.93–3.83)	0.076		
PFS	SLC2A1	rs4658	Smoker	0.61(0.38–0.99)	**0.044**	0.52(0.26–1.05)	0.069	0.51(0.21–1.25)	0.142
OS	AQP9	rs1867380	No Family history	0.50(0.20–1.24)	0.140	0.61(0.20–1.91)	0.390	0.15(0.02–0.89)	**0.037**
			LUAD	0.24(0.06–0.99)	**0.049**	0.26(0.05–1.43)	0.121	0.08(0.01–1.35)	0.079
			III/IV/ED	0.68(0.31–1.52)	0.348	0.85(0.33–2.18)	0.749	0.17(0.03–0.99)	**0.049**
OS	SLC2A1	rs3820589	No Family history	0.43(0.16–1.15)	0.093	0.30(0.10–0.97)	**0.043**		
OS	SLC22A2	rs316003	LUSC	12.43(1.62–94.27)	**0.015**	13.77(1.76–107.7)	**0.012**		
			Smoker	3.88(1.15–13.07)	**0.029**	4.13(1.16–14.78)	**0.029**		

Notes: Additive model: comparison between minor allele subjects and major allele subjects. Dominant model: comparison between minor allele carriers and major homozygous subjects. Recessive model: comparison between major allele carriers and minor homozygous subjects. p< 0.05 are indicated in bold text; *p< 0.05.
Abbreviations: OR, odds ratio; CI, confidence interval.

subsequently influenced cell differentiation and cell cycle arrest, thereby indirectly diminished the efficacy of neoadjuvant or adjuvant chemotherapy in lung cancer patients.[27,38,39] Indeed, our results showed that rs1867380 are related to prognosis of platinum-based chemotherapy. Furthermore, patients without family history in recessive model, patients who were diagnosed adenocarcinoma in additive model, patients who were advance stage (III/IV/ED) in recessive model demonstrated that association with OS.

ABCC2, known as multidrug resistance protein 2 (MRP2), play a role in transporting compound, chemoprotection and modulating the pharmacokinetics.[40] It has been reported that ABCC2 rs717620 was associated with response to platinum-based chemotherapy and pediatric heart transplant (PHTx).[30,41,42] ABCB10, as an ABC transporter, are located to mitochondria and involved in iron- and/or heme-related biological pathways.[43] ABCG2, also called BCRP – breast cancer resistance protein, was known to interact with dozens of anti-cancer agents that are ABCG2 substrates.[44]

This study analyzed a large numbers of transporter gene of genetic polymorphisms in lung cancer treated with platinum-based chemotherapy. However, this study has some limitations. First, further studies with a larger sample size studies would be helpful to validate the associations between genetic polymorphisms and prognosis. Second, some genetic polymorphisms showed statistical significance in our studies needs replication studies with other independent subjects.

Conclusion

In conclusion, we identified several genetic polymorphisms association with prognosis of platinum-based chemotherapy in lung cancer. The genetic polymorphisms of ABCG2 rs1448784 was significantly associated with PFS of lung cancer patients received platinum-based chemotherapy. The results of this study may contribute to the personalized treatment of lung cancer.

Data Sharing Statement

The raw data supporting the conclusion of this article will be made available by corresponding author on reasonable request.

Ethics Statement

All studies involving human participants were complied with the ethical standards of Committee of Xiangya School of Medicine, Central South University and Declaration of Helsinki.

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Disclosure

The authors declare that they have no competing interests in this work.

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