RESEARCH COMMUNICATION

Genetic Variants in the PI3K/PTEN/AKT/mTOR Pathway Predict Platinum-based Chemotherapy Response of Advanced Non-small Cell Lung Cancers in a Chinese Population

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Abstract

Objective: The PI3K/PTEN/AKT/mTOR signaling pathway has been implicated in resistance to cisplatin. In the current study, we determined whether common genetic variations in this pathway are associated with platinum-based chemotherapy response and clinical outcome in advanced non-small cell lung cancer (NSCLC) patients. Methods: Seven common single nucleotide polymorphisms (SNPs) in core genes of this pathway were genotyped in 199 patients and analyzed for associations with chemotherapy response, progression-free survival (PFS) and overall survival (OS). Results: Logistic regression analysis revealed an association between AKT1 rs2494752 and response to treatment. Patients carrying heterozygous AG had an increased risk of disease progression after two cycles of platinum-based chemotherapy compared to those with AA genotype (Adjusted odds ratio (OR)=2.18, 95% confidence interval (CI): 1.00-4.77, which remained significant in the stratified analyses). However, log-rank test and cox regression detected no association between these polymorphisms in the PI3K pathway genes and survival in advanced NSCLC patients. Conclusions: Our findings suggest that genetic variants in the PI3K/PTEN/AKT/mTOR pathway may predict platinum-based chemotherapy response in advanced NSCLC patients in a Chinese population.

Keywords: PI3K - AKT, mTOR - PTEN - polymorphism - NSCLC - chemotherapy

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Introduction

Lung cancer is the most common cancer worldwide with approximately 1.5 million newly diagnosed cases and 1 million deaths annually (Le Chevalier, 2010). Non-small cell lung cancer (NSCLC) accounts for 75%-85% of lung cancer and most NSCLC patients are diagnosed in advanced stage (Spiro and Silvestri, 2005). Although an improvement in NSCLC treatment could be achieved, especially in the last decade, chemotherapy remains the major component of the standard care in conjunction with radiation therapy. Platinum-based combination therapy is the first-line treatment for advanced NSCLC patients, however, the 5-year survival rate varies widely (3%-50%) depending on the clinical and biological behaviors of the tumor (Spira and Ettinger, 2004). Established factors predicting treatment outcome include gender, age, performance status and the tumor, lymph node, metastasis (TNM) staging system (Naruke et al., 2001). However, one's genetic background may also play an important role in modulating treatment response, especially because patients with the same stage and chemotherapy regimen often show different response rate. Therefore, identification of novel genetic biomarker to predict therapeutic response for more individualized treatment is of immense clinical benefit.

Platinum-based drugs are cytotoxic through the formation of platinum-DNA cross-links and adducts, causing cell cycle arrest and ultimately apoptosis if not properly repaired (Siddik, 2003). Wider application of cisplatin or carboplatin in NSCLC treatment has been impeded by intrinsic or acquired resistance (Kartalou and Essigmann, 2001). The PI3K/PTEN/AKT/mTOR pathway, fundamental for cell development, growth and survival, is one of the several pathways which involved in the processes of platinum-based drugs' cytotoxicity and resistance. Activation of PI3K takes place by binding with growth factors, such as epidermal growth factor receptor (EGFR) and vascular endothelial growth factor receptor (VEGFR), to their specific receptors, resulting in a kinase cascade through AKT and mTOR, generating downstream signals. PTEN is an antagonist of PI3K, which directly reverses the activity of PI3K by dephosphorylating the second messenger

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phosphatidylinositol-3,4,5-trisphosphate (PIP_3) into phosphatidylinositol-4,5-bisphosphate (PIP_2) (Wojtalla and Arcaro, 2011). The PI3K pathway is already known to be frequently altered in tumors, including carcinomas of the lung. Over-expression of PIK3CA (catalytic subunit of PI3K) was demonstrated in primary lung carcinomas and their metastases (Vandenbroucke et al., 2009). Additionally, genomic amplification of PIK3CA in NSCLC was common, occurring in 70% squamous cell carcinoma and 19% adenocarcinoma (Massion et al., 2004). Activation of AKT was also observed in primary NSCLC tumors, which was reported to be a poor prognostic factor for NSCLC patients with primary tumors or stage I disease (David et al., 2004; Tsurutani et al., 2006). Another downstream target of PI3K signaling mTOR, was shown to be activated in lung cancer cell lines (Balsara et al., 2004; Han et al., 2006), and more frequently activated in tumors with genetic alternations, such as EGFR mutations or PI3K/AKT over-expression (Conde et al., 2006). PTEN plays as negative controlling element, and its low expression displays constitutively activated PI3K signaling (David, 2001; Soria et al., 2002; Singhal et al., 2003; Kokubo et al., 2005; Marsit et al., 2005; Tang et al., 2006). Recently, it has been shown that the PI3K/PTEN/AKT/mTOR pathway contributes to the development of resistance to platinum-based chemotherapy (Lee et al., 2005; Mungamuri et al., 2006; Kim et al., 2007; Liu et al., 2007; Gagnon et al., 2008;). In addition, PI3K small molecule inhibitors LY294002 can dramatically increase NSCLC cell sensitivity to chemotherapy induced apoptosis (Brognard et al., 2001). Collectively, these evidence supports the importance of the PI3K/AKT pathway for proliferative and anti-apoptotic signaling in NSCLC.

Genetic variations within the PI3K/PTEN/AKT/mTOR pathway have recently been reported to associate with susceptibility of colorectal cancer and bladder cancer (Chen et al., 2009; Lin et al., 2010; Slattery et al., 2010). Additionally, polymorphisms within this pathway were also found to predict toxicity and distant progression in lung cancer patients receiving platinum-based chemotherapy (Pu et al., 2010). Because of the response to platinum-based chemotherapy varying from person to person, there is an urgent need for identification biomarkers to predict who will benefit from the chemotherapy to avoid over-treatment. In this study, we determined whether genetic variations in PIK3CA, AKT1, AKT2, FRAP1 (encoding for mTOR) and PTEN were associated with treatment response as well as prognosis in advanced NSCLC patients receiving platinum-based chemotherapy.

Materials and Methods

Study populations

All patients in the study were recruited from the First Affiliated Hospital of Nanjing Medical University (Jiangsu, China) between January 2004 and December 2010. All cases were newly diagnosed, histopathologically confirmed and without prior history of other cancers or previous chemo- or radio- therapy. Only inoperable, advanced NSCLC (IIIB–IV) patients were included in the study to avoid the potential confounding effect from surgery and clinical stage. Patients were interviewed face-to-face to collect demographic data including age, sex and smoking status. Those who had a low smoking frequency (<1 cigarette per day) and duration (<1 year) in their lifetime were defined as non-smokers; otherwise, they were classified as smokers. Each patient donated 5-ml venous blood after written informed consent was obtained. Finally, a total of 199 advanced NSCLC patients with available blood sample were included in our study. Patients' response to platinum-based (cisplatin or carboplatin) regimen was assessed after the first two or three cycles and determined by the Response Evaluation Criteria in Solid Tumors (RECIST) criteria 1.1 (Eisenhauer et al., 2009). All responses were re-evaluated at least 4 weeks after initial assessment. For data analysis, complete responses (CR), partial response (PR) and stable disease (SD) were combined as responders, progressive disease (PD) was grouped as non-responders. Follow-up was performed per three months from the time of enrollment till death or the latest follow-up. Progression-free survival (PFS) was defined as the time from first treatment to the date of disease progression (PD), death or last follow-up. Overall survival (OS) was calculated as the time between first dose and death or the last follows.

SNP selection and genotyping

Genomic DNA was extracted from a leukocyte pellet by traditional proteinase K digestion and followed by phenol-chloroform extraction and ethanol precipitation. We selected functional SNPs within the gene regions of five genes: PIK3CA, AKT1, AKT2, FRAP1 and PTEN according to (a) the minor allele frequency is greater than 5% among Chinese pupulation, (b) nonsynonymous SNP or SNP occurs at the 3'UTR, 5'UTR, or exons. However, no SNPs in PIK3CA and PTEN met the criteria. Finally, 7 SNPs in AKT1, AKT2 and FRAP1 were selected and then genotyped with TaqMan genotyping assays, using the ABI 7900 real-time PCR system (Applied Biosystems Inc., Foster City, CA). SDS allelic discrimination software (version 2.3, provided by ABI) was used for analysis of genotyping results. All the genotyping assays were performed with two blank (water) controls for quality control in each 384-well format and more than 10% samples were randomly selected to repeat, yielding a 100% concordant.

Statistical analysis

Hardy–Weinberg equilibrium was assessed by a goodness-of-fit χ^2 test. Odds ratios (ORs) and their 95% confidential intervals (CIs) were calculated as a measure of difference in the response rate using logistic regression analysis (responders vs. non-responders). The Kaplan-Meier and log-rank tests were used to assess the differences in PFS and OS. Median survival time (MST) was calculated, and mean survival time was presented when the MST could not be obtained. Cox proportional hazards model was applied to assess the hazard ratios (HRs) for PFS and OS. The adjustment factors included age, gender, smoking status, histology and stage. The

Table 1. Clinical Parameters and Paltinum-based Chemotherapy Response

Characteristics	Response			PFS				OS			
	Patients N (%)	PD N (%)	P[a]	Progression N (%)	MST[b] (months)	HR (95% CI)	Log-rank P	Progression N (%)	MST[b] (months)	HR (95% CI)	Log-rank P
Age (years)											
<=60	96 (48.2)	23 (24.0)	0.295	60 (62.5)	11.0	1.00 (reference)	0.603	25 (26.0)	32.4	1.00 (reference)	0.031
>60	103 (51.8)	18 (17.5)		70 (68.0)	10.0	1.10 (0.77-1.56)		42 (40.8)	21.7	1.74 (1.05-2.90)	
Gender											
Male	129 (64.8)	26 (20.2)	0.856	87 (67.4)	10.0	1.00 (reference)	0.106	48 (37.2)	22.4	1.00 (reference)	0.092
Female	70 (35.2)	15 (21.4)		43 (61.4)	13.8	0.73 (0.50-1.07)		19 (27.1)	31.2	0.63 (0.36-1.08)	
Smoking status											
Never	100 (50.3)	19 (19.0)	0.603	57 (57.0)	13.8	1.00 (reference)	<0.001	23 (23.0)	31.0	1.00 (reference)	<0.001
Smoker	99 (49.7)	22 (22.2)		73 (73.7)	9.0	2.01 (1.40-2.89)		44 (44.4)	16.9	2.74 (1.63-4.60)	
Histology type											
Squamous cell	57 (28.6)	13 (22.8)	0.573	39 (68.4)	9.8	1.00 (reference)	0.064	24 (42.1)	15.2	1.00 (reference)	0.043
Adenocarcinoma	137 (68.8)	28 (20.4)		89 (65.0)	10.1	0.70 (0.47-1.04)		41 (29.9)	30.8	0.53 (0.31-0.89)	
Others[c]	5 (2.5)	0 (0)		2 (40.0)	23.8	0.16 (0.02-1.17)		2 (40.0)	22.0	0.44 (0.10-1.96)	
Stage											
III	27 (13.6)	2 (7.4)	0.076	13 (48.1)	15.7	1.00 (reference)	0.378	6 (22.2)	18.0	1.00 (reference)	0.408
IV	172 (86.4)	39 (22.7)		117 (68.0)	10.0	1.30 (0.72-2.33)		61 (35.5)	27.8	1.43 (0.61-3.35)	

HR, hazard ratio; CI, confidence interval; MST, median survival time; PFS, progression-free survival; OS, overall survival. [a]P value for χ^2 test; [b]Mean survival time was provided when MST could not be calculated; [c]Other carcinomas include large cell, undifferentiated and mixed-cell carcinoma

Table 2. Treatment Characteristics of the Enrolled Patients

Chemotherapy regimens	Patients (N%)
DDP/CBP + TAX/TXT/DOC	129 (64.8)
DDP/CBP + GEM	36 (18.1)
DDP/CBP + Pemetrexed	21 (10.6)
DDP/CBP + NVB	13 (6.5)

DDP, cisplatin; CBP, carboplatin; TAX, taxol/paclitaxel; TXT, tanetere; DOC, docetaxel; GEM, gemcitabine; NVB, vinorelbine

statistical analyses were performed using Statistical Analysis System software (version 9.1.3, SAS Institute, Cary, NC). All P-values were two-sided, and P-value <0.05 was considered statistically significant.

Results

Patient characteristics and clinical features

The demographic characteristics and clinical information for the 199 NSCLC patients recruited in the study were summarized in Table 1. The median age was 60 years (range, 32-85 years). Of the 199 NSCLC patients, 129 (64.8%) were male and 99 (49.7%) were smokers. Among these patients, 137 (68.8%) were adenocarcinoma, 57 (28.6%) were squamous cell carcinomas and the others (5 patients) were large cell, undifferentiated and mixed-cell carcinomas. All the patients had advanced inoperable lung cancer, with 13.6% of stage IIIB and 86.4% of stage IV. The median PFS and OS for the 199 patients were 10.5 months (range, 1.0-62.0 months) and 22.4 months (range, 1.5-81.7 months), respectively. Patients who was diagnosed as lung adenocarcinoma or at an earlier age (<=60 years) may have a better OS (Log-rank p = 0.043 and 0.031, respectively). Smoking was an unfavorable factor for PFS (HR = 2.01, 95% CI: 1.40-2.89) and OS (HR = 2.74, 95% CI: 1.63-4.60). However, other clinical parameters were not associated with outcome of NSCLC patients.

Table 4. Stratified Analysis of rs2494752 Genotypes Associated Chemotherapy Response

Variable	AA response/patients	AG response/patients	Adjusted OR (95% CI)[a]	P
Age (years)				
<=60	32/28	31/46	2.56 (0.86-7.62)	0.091
>60	35/41	37/48	2.34 (0.70-7.84)	0.166
Gender				
Male	43/49	43/61	3.35 (1.16-9.68)	0.025
Female	24/30	25/33	1.02 (0.28-3.68)	0.982
Smoking status				
Never	35/42	37/48	1.25 (0.42-3.71)	0.693
Smoker	32/37	31/46	3.71 (1.14-12.14)	0.030
Histology type				
Squamous cell	19/25	20/27	1.08 (0.27-4.27)	0.910
Adenocarcinoma	45/51	47/66	3.20 (1.15-8.91)	0.026
Stage				
III	9/10	12/13	--	--
IV	58/69	56/81	2.38 (1.05-5.39)	0.037

OR, odds ratio; CI, confidence interval; [a]Adjusted for age, gender, smoking status, histology and stage

Polymorphisms and treatment response

All patients had received platinum-based chemotherapy: 129 received TP/TC (DDP/CBP plus taxol/taxotere/docetaxel), 36 had GP/GC regimens (DDP/CBP plus gemcitabine), 21 had NP/NC (DDP/CBP plus vinorelbine), and 13 were given DDP/CBP plus pemetrexed regimens (Table 2). The concrete dosage were as follows: DDP 75 mg/m^2 on Day 1; CBP area under the curve (AUC) 5-6 g on Day 1; taxol 175 mg/m^2 on Day 1 (kept for 3h); taxotere 75 mg/m^2 on Day 1 (kept for 1h); docetaxel 60 mg/m^2 on Day 1 (kept for 1h); gemcitabine 1250 mg/m^2 on Days 1 and 8; vinorelbine 25 mg/m^2 on Days 1 and 8; pemetrexed 800 mg/m^2 on Day 1. All the chemotherapeutic agents were administered intravenously. Treatment cycles were repeated every 3-4 weeks, for 3-6 cycles, unless unacceptable toxicity or disease progression appeared.

Table 3. Genotyping of SNPs in PI3K Pathway and Their Associations with Chemotherapy Response

Gene	Genotype	Patients(N%)	PR+SD/PD	Crude OR (95% CI)	Adjusted OR (95% CI)[a]	P
AKT1	rs2498786					
	GG	122 (63.5)	98/24	1.00 (reference)	1.00 (reference)	
	GC	57 (29.7)	42/15	1.46 (0.70-3.06)	1.61 (0.74-3.48)	0.229
	CC	13 (6.8)	12/1	0.34 (0.04-2.75)	0.40 (0.05-3.29)	0.390
	CC+GC	70 (36.5)	54/16	1.21 (0.59-2.47)	1.34 (0.64-2.80)	0.445
AKT1	rs2494752					
	AA	79 (40.1)	67/12	1.00 (reference)	1.00 (reference)	
	AG	95 (47.7)	68/26	2.14(1.00-4.58)	2.18 (1.00-4.77)	0.050
	GG	23 (12.2)	22/2	0.51 (0.11-2.45)	0.50 (0.10-2.45)	0.391
	GG+AG	118 (59.9)	90/28	1.74 (0.82-3.67)	1.76 (0.82-3.78)	0.145
AKT1	rs2494750					
	GG	144 (73.8)	114/30	1.00 (reference)	1.00 (reference)	
	GC	47 (23.6)	37/9	0.92 (0.40-2.12)	0.83 (0.35-1.95)	0.670
	CC	4 (2.6)	4/1	0.95 (0.10-8.82)	0.68 (0.07-6.66)	0.744
	CC+GC	51 (26.2)	41/10	0.92 (0.42-2.06)	0.81 (0.36-1.85)	0.624
AKT1	rs74090038					
	CC	95 (48.2)	80/15	1.00 (reference)	1.00 (reference)	
	CT	82 (41.6)	60/22	1.96 (0.94-4.09)	1.93 (0.90-4.15)	0.090
	TT	20 (10.2)	18/2	0.59 (0.12-2.82)	0.55 (0.11-2.70)	0.463
	TT+CT	102 (51.8)	78/24	1.64 (0.80-3.36)	1.59 (0.76-3.32)	0.218
AKT2	rs34716810					
	TT	146 (74.5)	115/31	1.00 (reference)	1.00 (reference)	
	TC	46 (23.5)	38/8	0.78 (0.33-1.85)	0.70 (0.29-1.69)	0.426
	CC	4 (2.0)	3/1	1.24 (0.12-12.31)	0.99 (0.09-10.55)	0.996
	CC+TC	50 (25.5)	41/9	0.81 (0.36-1.86)	0.72 (0.31-1.68)	0.451
AKT2	rs62107593					
	CC	77 (39.7)	62/15	1.00 (reference)	1.00 (reference)	
	CG	86 (44.3)	64/22	1.42 (0.68-2.99)	1.30 (0.60-2.78)	0.508
	GG	31 (16.0)	27/4	0.61 (0.19-2.02)	0.49 (0.14-1.65)	0.247
	GG+CG	117 (60.3)	91/26	1.18 (0.58-2.41)	1.04 (0.50-2.17)	0.913
FRAP1	rs12139042					
	GG	171 (83.8)	136/35	1.00 (reference)	1.00 (reference)	
	GA	23 (11.3)	18/5	1.08 (0.38-3.11)	1.18 (0.39-3.56)	0.767
	AA	3 (1.5)	2/1	1.94 (0.17-22.05)	2.41 (0.19-30.57)	0.497
	AA+AG	26 (8.4)	20/6	0.63 (0.13-3.16)	0.52 (0.10-2.78)	0.447

OR, odds ratio; CI, confidence interval; [a]Adjusted for age, gender, smoking status, histology and stage

Overall, no patients had complete response. 69 (34.7%) patients demonstrated PR, 89 (44.7%) showed SD and 41 (21.6%) patients had PD. We combined PR and SD as responders; PD patients were grouped as non-responders. The 7 SNPs of the PI3K pathway were successfully amplified from more than 95% of the patients. Genotype frequencies are in agreement with those expected according to the Hardy-Weinberg equilibrium model. The associations between SNPs and platinum-based chemotherapy response were analyzed and showed in Table 3. One SNP, AKT1: rs2494752 showed an association with poorer treatment response. Patients carrying heterozygous AG had a significantly increased risk of disease progression after two cycles of platinum-based chemotherapy compared to those with AA genotype (OR=2.14, 95% CI: 1.00-4.58). This association remained significant after adjusted for age, gender, smoking status, histology and clinical stage (Adjusted OR=2.18, 95% CI: 1.00-4.77). However, no significant associations were detected between other polymorphisms in the PI3K pathway and treatment response.

The associations between AKT1 rs2494752 polymorphism and platinum-based chemotherapy response among advanced NSCLC patients were further stratified by age, gender, smoking status, histology and clinical stage. As shown in Table 4, the association remained significant among male patients (OR=3.35, 95% CI: 1.16-9.68), smokers (OR=3.71, 95% CI: 1.14-12.14), individuals with adenocarcinoma (OR=3.20, 95% CI: 1.15-8.91) and clinical stage IV (OR=2.38, 95% CI: 1.05-5.39). No significant heterogeneity existed in every stratum.

Polymorphisms and survival

Log-rank test failed to detect any association between polymorphisms in the PI3K pathway and prognosis of advanced NSCLC patients. A univariate analysis and multivariate survival analysis including age, gender, smoking status, histology and clinical stage showed that there was no significant association of any genotypes with PFS or OS.

Discussion

The PI3K/PTEN/AKT/mTOR pathway regulates various cellular processes and its deregulation may lead

to carcinogenesis and cancer progression. This pathway is often activated in several cancer types, including lung cancer, and has been shown to be important in the development of resistance to platinum-based chemotherapeutic agents. As there has been an increasing application of the pathway-based approach in cancer genetic and association studies (Subramanian et al., 2005), we selected common functional SNPs for five genes in the PI3K pathway to determine whether genetic variations in this pathway were associated with variation in chemotherapy response and prognosis. Significant association was observed between AKT1 rs2494752 and platinum-based chemotherapy response, which remained significant in the stratified analyses. Whereas no association was detected between these polymorphisms in the PI3K pathway genes and survival in advanced NSCLC patients. To our knowledge, this is the first study to investigate the association between genetic variations in PI3K pathway and clinical outcome of NSCLC patients in a Chinese population.

Recently, several publications have reported genetic variants in the PI3K pathway could modify cancer susceptibility and prognosis. In Slattery et al.' s study, a strong association was observed for PIK3CA polymorphism and colorectal cancer risk, and a SNP in FRAP1 was associated with microsatellite instability (MSI)+ colon tumors (Slattery et al., 2010). Pooled analysis of PI3K pathway variants and prostate cancer susceptibility showed the polymorphisms in the PIK3C2B gene were correlated with elevated prostate cancer risk, especially for familial and early onset disease (Koutros et al., 2010). In another study that evaluated the association between a comprehensive set of SNPs in the PI3K pathway genes and bladder cancer, 4 polymorphisms in the RAPTOR (regulatory associated protein of mTOR) was found to associate with elevated bladder cancer risk, especially among male and older populations (Chen et al., 2009). Moreover, when assessed the joint effects of polymorhpisms in RAPTOR with physical activity and energy intake, subjects in the worst energy balance category (carrying >= 7 unfavorable genotypes, low physical activity, and high energy intake) had 21.93-fold increased risk (Lin et al., 2010). Three genetic variations in AKT2, PIK3R1 and RAPTOR were also found to be significantly associated with muscle invasive and metastatic bladder cancer patients' survival. In combined analysis, a cumulative effect of these three SNPs on survival was found (Chen et al., 2010). Additionally, polymorphisms within the PI3K pathway were also found to predict treatment response and clinical outcome in esophageal cancer patients (Hildebrandt et al., 2009). As for lung cancer patients receiving platinum-based chemotherapy, tagging SNPs in PIK3CA and PTEN were associated with increased or reduced risk for chemotherapeutic toxicity respectively. Three polymorphisms in AKT1 were found to result in significantly decreased risk of distant progression in patients carrying at least one variant allele (Pu et al., 2010).

Interestingly, we found AKT1 rs2494752 could predict platinum-based chemotherapy response. This is of particularly intriguing because AKT plays a critical role in regulating cell survival, proliferation and protein synthesis (Bellacosa et al., 2005). AKT activation due to overexpression or gene amplification is a common molecular alteration during carcinogenesis, and constitutively activated AKT in NSCLC results in cell survival by blocking induction of apoptosis (Brognard et al., 2001). In addition, forced expression of AKT has been shown to be involved in resistance to cisplatin and other common chemotherapeutic agents for lung, ovarian and uterine cancer (Lee et al., 2005; Kim et al., 2007; Liu et al., 2007; Gagnon et al., 2008). AKT1 rs2494752 is located in the 5' UTR of AKT1 and may modify the expression levels of AKT1 gene by interfere its' binding with transcription factors. We found individuals carrying heterozygous of rs2494752 had a poorer response to platinum-based chemotherapeutic agents. The directionality of the effect indicates that this functional variant may amplify AKT1 activity causing increased cell survival signals against cytotoxic effect of cisplatin. Further studies are warranted to validate the association between this polymorphism and chemotherapy response.

In our current study, we did not find any association between polymorphisms in core functional components of PI3K pathway and advanced NSCLC patients' survival. This is consist with a previous study which found none of the SNPs in these genes to be an independent prognostic marker for Korean colorectal cancer patients after surgical (Kim et al., 2010). However, this pathway is complex, with several other genes warranting investigation on the basis of the results of our study. PDK1 and PDK2 are phosphoinositide-dependent kineses responsible for phosphorylating AKT, resulting in AKT activation (Alessi et al., 1997). Tuberous sclerosis complex (TSC) tumor suppressor genes, TSC1 and TSC2, are directly downstream of AKT. TSC2 phosphorylated by AKT inhibits the function of this complex, allowing for the activation of mTOR (Tee et al., 2002). Genetic variations in these genes may contribute to variation in clinical outcome, especially in combination with genetically altered AKT.

In conclusion, although based on a small sample size, our findings suggest that genetic variants in the PI3K/PTEN/AKT/mTOR pathway may predict platinum-based chemotherapy response in advanced NSCLC patients in a Chinese population. Our results need further validation from larger patient cohorts and functional evaluations for individualized treatment.

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