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ORIGINAL RESEARCH

The Effects of WISP1 Polymorphisms on the Prognosis of Lung Cancer Patients with Platinum-Based Chemotherapy

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Purpose: To investigate the relationships between Wnt1 inducible signaling pathway protein 1 (WISP1) polymorphisms and the prognosis of platinum-based chemotherapy in lung cancer patients.

Patients and Methods: A total of 363 lung cancer patients were recruited in this study. All of them received at least two cycles of platinum-based chemotherapy. We used unconditional logistic regression analysis to assess the associations of 39 single nucleotide polymorphisms in WISP1 gene with platinum-based chemotherapy prognosis.

Results: The results indicated that patients carried rs2929973 GT or GG genotypes had increased risk of disease progression (HR = 0.712, 95% CI = 0.553–0.916, P = 0.015). Patients with rs2977551 TT genotype had a significantly decreased risk of progression-free survival than patients carrying CT or CC genotype (HR = 0.723, 95% CI = 0.561–0.932, P = 0.032) and overall survival (HR = 0.725, 95% CI = 0.552–0.913, P = 0.045). For rs2977549, patients carrying TT genotype had a significantly longer progression-free survival than patients with CC or CT genotypes (HR = 0.708, 95% CI = 0.550–0.912, P = 0.017). Among of them, rs16904853, rs10956697, rs2929965, rs2929973, rs7828685, rs2977551 and rs2977549 were related to progression-free survival, and rs10956697 and rs2977551 were related to overall survival in subgroup analyses, respectively.

Conclusion: WISP1 rs2929973, rs2977551 and rs2977549 may be contributed to a potential candidate biomarker for prediction of platinum-based chemotherapy prognosis in lung cancer patients.

Keywords: lung cancer, platinum-based chemotherapy, prognosis, genetic polymorphism, WISP1

Introduction

Lung cancer is the most common incidence and the leading cause of cancer related deaths worldwide.[1] Two major types of lung cancer are classified as small cell lung cancer (SCLC) and non–small cell lung cancer and (NSCLC).[2] NSCLC patients, approximately 85% of the total lung cancer cases, are often diagnosed in advanced stage and metastatic.[3,4] At present, the main therapies of lung cancer are surgery, radiation therapy, immunotherapy and chemotherapy.[5] Immunomodulatory therapies have been approved as second-line agents for patients with advanced lung cancer as well as first-line therapy for patients with high level (>50%) of PD-L1 expression and absence of sensitizing EGFR mutations or ALK rearrangements.[6] However, lung cancer patients with advanced NSCLC who do not fit an approved

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molecular targeted therapy, the standard first-line treatment remains platinum-based doublet therapy with or without bevacizumab.[5] The five-year overall survival rate for lung cancer is still approximately 18%, the prognosis for the advanced-stage disease is even poorer, with a median overall survival of approximately one year.[7,8]

Wnt1 inducible signaling pathway protein 1 (WISP1), as a member of the CCN family of proteins, is known as CCN4.[9] The human WISP1 gene is located on chromosome 8q24.1–q24.3.[10] The CCN family of proteins possess six secreted extracellular matrix associated proteins. Each family member contains four structural domains: an insulin-like growth factor binding protein-like module (IGFBP), a von Willebrand factor type C repeat (VWC), a thrombospondin domain (TSP1), and a C-terminal cysteine-knot-containing (CT) domain.[11] Wnt1 signaling pathways can modulate multiple processes that involve neuronal development, angiogenesis, immune cell modulation, tumorigenesis, and stem cell proliferation.[12–15] Activation of WISP1 transcript and protein were detected in carcinomas in vivo, such as hepatocellular carcinoma, colon adenocarcinomas, lung carcinoma, and breast cancer.[10,16–18] However, the role of WISP1 in clinical lung cancer with platinum-based chemotherapy still needs to be clarified.

Single Nucleotide Polymorphisms (SNPs) represent the most common type of variation in the human genome, a single base in the DNA differs from the usual base at that position. SNPs are the marker of choice in genetic analysis and also useful in locating genes association with diseases.[19] While the reason of SNPs effects on gene expression, protein binding is not completely understood.[20] Previous study reported that WISP1 has been detected in scirrhous gastric carcinoma and invasive cholangiocarcinoma.[21] Overexpression of WISP1 variants increases the growth rate of mouse embryonic fibroblasts rat kidney fibroblasts, hBMSCs and human esophageal cancer cells.[21,22] In lung cancer cells overexpression WISP1 leads to an inhibition in vitro cell invasion and motility, as well as lung metastasis.[17] The roles of WISP1 were marked varieties in difference type of cancers. For example, high expression levels of WISP1 were correlated with poor prognosis in breast,[18] rectal,[23] esophageal cancer[24] and colon cancer,[25] but WISP1 expressed lower levels in melanoma with poor prognosis.[26] Despite the role of WISP1 affects lung cancer progression is not clear.

In the present study, we evaluated whether genotypes of WISP1 in lung cancer patients could be involved in prognosis of lung cancer patients with platinum-based chemotherapy.

Methods and Materials

Study Populations

The study subjects consist of 363 patients that are diagnosed lung cancer in the Affiliated Cancer Hospital or Xiangya Hospital of Central South University (Changsha, Hunan, China) during 2011 to 2013. Patients clinical and laboratory findings were collected from medical records. The recruitment criteria included the following: Eligible patients were histologically or cytologically proven lung cancer who had experienced disease progression. Patients with a history of previous malignant tumor or concomitant malignancies, metastases were excluded from this cohort. All patients were treated with platinum-based chemotherapy at least 2 cycles and were not given radiotherapy and/or biological therapy before and during chemotherapy. All patients were signed informed consents were obtained from all study participants before chemotherapy. The clinical and laboratory data including age, sex, smoking history, TNM stage, histological type and stage, chemotherapy regimens were collected from medical records.

The study was in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration, and the study protocol was approved by the Ethics Committee of Xiangya School of Medicine, Central South University with a registration number of CTXY-110008-2.

SNP Selection, DNA Extraction and Genotyping

According to the data from the HapMap, or previous studies, we selected 39 SNPs (Table S1) of the WISP1 gene which described previously.[27,28] In brief, the following criteria: (1) A total of them with minor allele frequency (MAF) ≥0.05 in the Chinese population were selected. (2) The tag SNP selection was performed using the Tagger program implemented in Haploview version 4.2. (3) SNPs located in the promoter region, exon region, and the 3′ untranslated region (UTR). Genomic DNA was extracted from the whole blood by using the FlexiGene DNA Kit (Qiagen, Hilden, Germany) according to the manufacturer's instructions. The DNA sample was stored at −20 °C before usage. WISP1 polymorphism was

genotyped using the Sequenom Mass ARRAY System (Sequenom, San Diego, CA, USA).

Statistical Analysis

The statistical analysis was conducted by the SPSS version 25.0 (SPSS Inc., Chicago, IL, USA) and GraphPad Prism (version 8, GraphPad Software Inc., San Diego, CA). We used Cox proportional hazards regression model to analysis each genetic variant and OS/PFS, measured as HRs with their corresponding 95% CIs. The covariates used for adjusted HR for PFS included age, gender, smoking status, histology, and clinical stage between the OS and PFS. Kaplan-Meier test was used to assess each genetic variant on the cumulative probability of PFS and OS. All association analyses were evaluated by three models including additive, dominant, and recessive. All P-values presented were two-sided, and a level of $P < 0.05$ was considered statistically significant.

Results

Characteristics and Survival Status of the Lung Cancer Patients

In order to investigate the association of WISP1 Polymorphisms and clinical results of platinum-based chemotherapy, the present study consisted of 363 patients diagnosed with lung cancer, who had DNA samples, complete data on demographic, clinical characteristics, progression free survival (PFS) and overall survival (OS). All patients who received at least 2 cycles of platinum-based chemotherapy were enrolled to investigate the association of WISP1 polymorphisms with chemotherapy. As shown in Table 1, 289 were males and 74 were females, with the median age of cohort was 56 (a range of 21 to 77 years old). The patients who ever or current smokers accounted for 63.6%, and the ones who were never smokers accounted for 36.4%. For the patient group, 244 (67.2%) patients with presented advanced NSCLC and 119 (32.8%) patients with SCLC, and most of which were with stage III/IV (65.8%).

Association of WISP1 Polymorphisms with Platinum-based Chemotherapy Prognosis in the Lung Cancer Patients

To investigate the association between WISP1 Polymorphisms and the prognosis of lung cancer patients received platinum-based chemotherapy, we selected 39 SNPs and those SNPs under investigation are shown in Table 2. After adjustments for age, sex, smoking status, histological type and TNM stage 7 SNPs (rs16904853, rs10956697, rs2929965, rs2929973, rs7828685, rs2977551, rs2977549) consistently showed a significant association with PFS and / or OS in lung cancer patients using Log rank test and multivariate Cox regression analysis (Table 2). Unconditional logistic regression analysis with adjustments revealed that WISP1 rs16904853 (P for log-rank=0.010), rs10956697 (P for log-rank=0.014), rs2929965 (P for log-rank=0.036), rs7828685 (P for log-rank=0.025) were significantly associated with lung cancer PFS in the additive model. WISP1 rs10956697 (P for log-rank=0.004), rs2929973 (P for log-rank=0.015), rs7828685 (P for log-rank=0.027), rs2977551 (P for log-rank=0.032), rs2977549 (P for log-rank=0.017) were significantly related to lung cancer PFS in the dominant model. rs16904853 (P for log-rank=0.003), rs2929965 (P for log-rank=0.013), rs7828685 (P for log-rank =0.023) were significant association with PFS in the recessive model (Figure 1). For OS analysis, our results demonstrated that lung cancer patients with rs10956697 were significantly related to better OS (HR=0.728, 95% CI=0.557–0.953, P =0.021) in the dominant model. Additionally, patients carrying TT genotype in rs2977551 were significantly related to better OS (HR=0.725, 95% CI=0.552–0.913, P =0.020) (Table 2) (Figure 2).

Association Between SNPs and Lung Cancer Progression

Next, we evaluated the relationship between the single nucleotide polymorphisms were related to tumor progression with patients receiving platinum-based chemotherapy. As described in Table 3, the rs2929973, rs2977551 and rs2977549 in WISP1 gene still significantly contributed to T stage of lung cancer patients. Both in the univariate Cox regression analysis and after adjusted by age, gender, smoking status, histological type and stage, we found that patients carrying GT or GG genotype in rs2929973 were a lower hazard to early T stage (T1 or T2) when compared with TT genotype (OR=0.486, 95% CI=0.271–0.871, P =0.015). Patients who carried the rs2977551 CT or CC genotype had a more significantly association with early T stage than patients with TT genotype (OR=0.428, 95% CI=0.238–0.771, P =0.005). For rs2977549 compared with CT or CC genotype carries, individuals with TT genotype tended to be association with early T stage (OR=0.438, 95% CI=0.246–0.781, P =0.005).

Table 1 Association Between Clinical Characteristics and PFS and OS of Patients with Lung Cancer

Variables	Overall Survival (OS)					Progression-Free Survival (PFS)				
	MST (Year)	Death/Total	P1	HR (95% CI)	P2	MST (Year)	Progression/Total	P1	HR (95% CI)	P2
Age (year)										
<60	4.28	159/164	0.133	Ref.	0.134	4.32	178/242	0.611	Ref.	0.611
≥60	4.33	94/97		0.82(0.63–1.06)		4.07	102/130		1.06(0.83–1.36)	
Gender										
Female	4.62	49/51	0.218	Ref.	0.219	4.98	44/76	0.287	Ref.	0.288
Male	4.10	204/210		0.82(0.60–1.12)		3.89	135/296		0.85(0.64–1.14)	
Smoking status										
Never smoker	4.62	91/93	0.393	Ref.	0.394	4.83	101/137	0.226	Ref.	0.227
Ever smoker	3.72	161/167		0.89(0.69–1.16)		3.72	178/234		0.86(0.67–1.10)	
Histology										
NSCLC	4.36	137/179	0.668	Ref.	0.668	3.92	193/250	0.289	Ref.	0.289
SCLC	4.06	77/79		1.06(0.81–1.39)		4.81	87/122		0.87(0.68–1.12)	
TNM stage										
I/II	3.94	6/6	0.764	Ref.	0.765	4.07	7/11	0.416	Ref.	0.418
III/IV	4.42	169/175		0.88(0.39–2.00)		3.89	148/239		1.37(0.64–2.91)	
LD	3.50	33/34	0.905	Ref.	0.905	4.31	37/52	0.862	Ref.	0.862
ED	4.10	43/44		1.03(0.65–1.63)		4.89	49/67		1.04(0.68–1.60)	

Notes: P1, P-value for Log rank test; P2, P-value for univariate Cox hazards regression analysis; P < 0.05 are indicated in bold text.
Abbreviations: MST, median survival time (year); HR, hazard ratio; CI, confidence interval; Ref., reference; NSCLC, lung adenocarcinoma; SCLC, lung squamous cell carcinoma.

Subgroup Analysis of Association Between WISP1 Polymorphisms and Prognosis

To better explore the WISP1 polymorphisms with OS and PFS of patients received chemotherapy, stratified analysis was performed based on the ages, gender, smoking status, histological type and TNM stage.

As shown in Table 4, the risk genotype group carries with rs2929973 GT or GG genotypes tended to have a significantly increased risk of disease progression and PFS in subgroups of patients with ≤60 years old. For patients who had never smoked, carrying TT genotype had a significantly decreased risk of death (HR=0.617, 95% CI=0.383–0.994, *P* =0.047). In the presence of GT or GG genotype, patients with NSCLC were markedly increased than those with TT genotype (HR=0.693, 95% CI=0.501–0.959, *P*=0.027). For patients who had TNM stage III/IV, carrying GT or GG genotype had a significantly increased risk of death (HR=0.649, 95% CI=0.470–0.896, *P* =0.009) and PFS (HR=1.377, 95% CI=1.024–1.852, *P* =0.034). For rs2977551, we found that carriers of CT or CC genotype tended to have a significantly increased risk of PFS in subgroups of younger (≤60 years old) (HR=1.413, 95% CI=1.022–1.954, *P* =0.037), never smokers (HR=1.572, 95% CI=1.007–2.455, *P* =0.047). For rs2977549, the risk genotype group carriers with CT or CC genotypes tended to have a significantly increased risk of disease progression in subgroups of patients with ≤60 years old. Patients carrying TT genotype tend to a lower risk of PFS (HR=1.480, 95% CI=1.071–2.047, *P* =0.018). Compared with CT or CC genotype tend to be sensitive to platinum-based chemotherapy, patients with NSCLC were markedly increased risk of death than those with TT genotype (HR=1.502, 95% CI=1.087–2.075, *P*=0.014) and PFS (HR=1.358, 95% CI=1.005–1.835, *P*=0.046). For patients who had TNM stage III/IV, rs2977549 carrying TT genotype had a significantly decreased risk of death (HR=1.601, 95% CI=1.157–2.216, *P* =0.005) and PFS (HR=1.419, 95% CI=1.053–1.913, *P* =0.022).

Discussion

Our present study systematically investigated the clinical significances of the WISP1 polymorphisms on the prognosis of lung cancer patients that underwent platinum-based chemotherapy. In the current study, we found that WISP1 rs2929973, rs2977551 and rs2977549 contribute to a significantly correlated with platinum-based prognosis.

Table 2 Association Between Single Nucleotide Polymorphisms (SNPs) and Clinical Outcomes in Lung Cancer Patients

Gene/SNP	Model	Genotype	Progression-Free Survival (PFS)					Overall Survival (OS)				
			Progression/Total	MST (Month)	P1	HR (95% CI)	P2	Death/Total	MST (Month)	P1	HR (95% CI)	P2
rs16904853	Additive	CC CT TT	65/95 133/181 71/82	4.964 4.310 2.397	**0.010**	Ref. 0.581(0.409–0.825) 0.694(0.515–0.936)	 0.004 0.011	58/71 120/135 65/70	4.918 4.422 4.362	0.238	Ref. 0.711(0.497–1.017) 0.907(0.667–1.233)	 0.155 0.062
	Dominant	CC CT/TT	65/95 204/263	4.964 3.800	0.105	Ref. 0.790(0.597–1.047)	0.101	58/71 185/205	4.918 4.392	0.123	Ref. 1.320(0.979–1.780)	0.069
	Recessive	CC/CT TT	198/276 71/82	4.581 2.397	**0.003**	Ref. 0.658(0.500–0.866)	0.003	178/206 65/70	4.660 4.362	0.232	Ref. 0.831(0.623–1.108)	0.207
rs10956697	Additive	CC CA AA	105/155 128/160 35/42	4.964 3.279 2.871	**0.014**	Ref. 0.609(0.411–0.904) 0.902(0.616–1.320)	 0.050 0.140	93/113 115/127 30/33	4.921 4.447 3.942	0.120	Ref. 0.617(0.402–0.948) 0.817(0.539–1.239)	 0.042 0.028
	Dominant	CC CA/AA	105/155 163/202	4.964 3.107	**0.004**	Ref. 0.662(0.515–0.852)	0.001	93/113 145/160	4.921 4.416	**0.045**	Ref. 0.728(0.557–0.953)	0.021
	Recessive	CC/CA AA	233/315 35/42	4.362 2.871	0.169	Ref. 0.749(0.520–1.078)	0.421	208/240 30/33	4.767 3.942	0.289	Ref. 0.717(0.482–1.069)	0.102
rs2929965	Additive	CC CT TT	75/110 140/188 50/57	4.833 4.416 3.260	**0.036**	Ref. 0.600(0.416–0.866) 0.622(0.473–0.925)	 0.018 0.060	65/80 127/144 46/48	4.833 4.529 4.625	0.361	Ref. 0.731(0.499–1.070) 0.793(0.562–1.119)	 0.258 0.107
	Dominant	CC CT/TT	75/110 190/245	4.833 4.074	0.163	Ref. 0.826(0.630–1.082)	0.165	65/80 173/192	4.833 4.581	0.313	Ref. 0.870(0.653–1.159)	0.340
	Recessive	CC/CT TT	215/298 50/57	4.523 3.260	**0.013**	Ref. 0.638(0.464–0.878)	0.006	192/224 46/48	4.619 4.625	0.208	Ref. 0.770(0.555–1.069)	0.080
rs2929973	Additive	TT GT GG	98/146 145/179 30/37	4.811 3.380 3.534	0.051	Ref. 0.724(0.478–1.099) 1.021(0.685–1.522)	 0.031 0.129	85/108 132/145 26/28	4.833 4.529 4.858	0.154	Ref. 0.741(0.474–1.159) 0.978(0.638–1.500)	 0.124 0.189
	Dominant	TT GT/GG	98/146 175/216	4.811 3.800	**0.015**	Ref. 0.712(0.553–0.916)	0.008	85/108 158/173	4.833 4.619	0.059	Ref. 0.755(0.576–0.989)	**0.014**
	Recessive	TT/GT GG	243/325 30/37	4.195 3.534	0.596	Ref. 0.878(0.579–1.291)	0.509	217/250 26/28	4.581 4.858	0.894	Ref. 0.871(0.576–1.316)	0.511

(*Continued*)

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Table 2 (Continued).

Gene/SNP	Model	Genotype	Progression-Free Survival (PFS)					Overall Survival (OS)				
			Progression/Total	MST (Month)	P1	HR (95% CI)	P2	Death/Total	MST (Month)	P1	HR (95% CI)	P2
rs7828685	Additive	AA GA GG	101/145 118/155 54/62	4.918 3.888 2.151	**0.025**	Ref. 0.617(0.441–0.864) 0.807(0.581–1.120)	 0.014 0.005	90/108 107/120 46/49	4.844 4.619 3.910	0.163	Ref. 0.699(0.488–1.001) 0.898(0.633–1.275)	 0.093 0.051
	Dominant	AA GA/GG	101/145 172/217	4.918 3.249	**0.027**	Ref. 0.718(0.558–0.923)	0.010	90/108 153/169	4.844 4.447	0.080	Ref. 1.327(1.017–1.732)	0.037
	Recessive	AA/GA GG	219/300 54/62	4.416 2.151	**0.023**	Ref. 0.706(0.522–0.956)	0.024	197/228 46/49	4.789 3.910	0.177	Ref. 1.327(1.017–1.732)	0.163
rs2977551	Additive	TT CT CC	96/142 132/169 46/55	4.885 4.049 3.107	0.086	Ref. 0.674(0.471–0.964) 0.911(0.648–1.281)	 0.037 0.031	83/102 121/135 41/43	4.918 4.619 3.907	0.124	Ref. 0.658(0.449–0.965) 0.881(0.641–1.263)	 0.052 0.032
	Dominant	TT CT/CC	96/142 178/224	4.885 3.723	**0.032**	Ref. 0.723(0.561–0.932)	0.012	83/102 162/178	4.918 4.447	**0.045**	Ref. 0.725(0.552–0.913)	0.020
	Recessive	TT/CT CC	228/311 46/55	4.700 4.457	0.204	Ref. 0.795(0.576–1.097)	0.163	204/237 41/43	4.811 3.907	0.296	Ref. 0.777(0.552–1.093)	0.148
rs2977549	Additive	TT CT CC	96/141 119/149 53/63	4.921 3.066 3.279	0.053	Ref. 0.691(0.492–0.971) 0.966(0.698–1.335)	 0.027 0.832	82/100 116/130 49/53	4.918 4.416 4.625	0.145	Ref. 0.716(0.500–1.025) 0.948(0.767–1.328)	 0.094 0.068
	Dominant	TT CT/CC	96/141 180/227	4.921 3.534	**0.017**	Ref. 0.708(0.550–0.912)	0.059	82/100 165/181	4.918 4.447	0.055	Ref. 0.744(0.567–0.974)	0.032
	Recessive	TT/CT CC	223/305 53/63	4.362 3.279	0.213	Ref. 0.826(0.610–1.119)	0.373	198/230 49/51	4.660 4.625	0.271	Ref. 0.837(0.611–1.148)	0.271

Notes: P1, *P*-value for Log rank test; P2, *P*-value for multivariate Cox hazards regression with adjustment for age, gender, and histology; $P < 0.05$ are indicated in bold text; 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.
Abbreviations: MST, median survival time (year); HR, hazard ratio; CI, confidence interval.

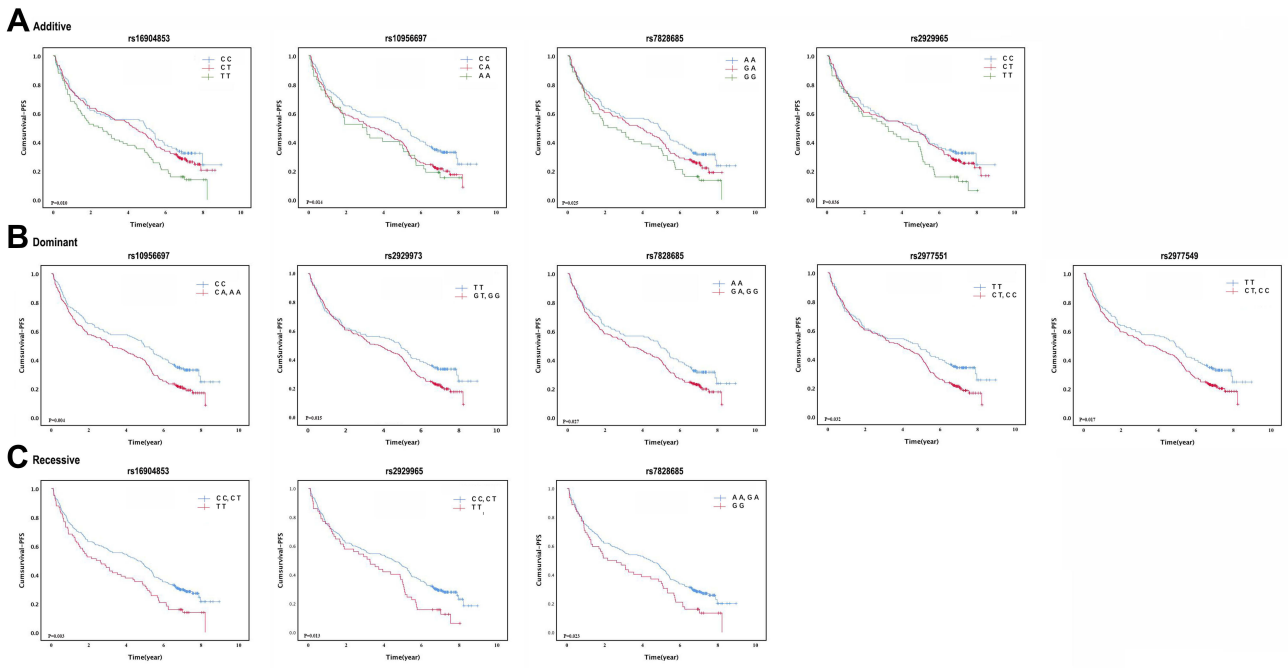

Figure 1 Kaplan–Meier plots of lung cancer patients with different genotypes of in WISP1 gene. (**A**) PFS of lung cancer patients by rs16904853, rs10956697, rs7828685, rs2929965 genotypes using additive model. (**B**) PFS of lung cancer patients by rs10956697, rs2929973, rs7828685, rs2977551, rs2977549 genotypes using dominant model. (**C**) PFS of lung cancer patients by rs16904853, rs2929965, rs7828685 genotypes using recessive model.

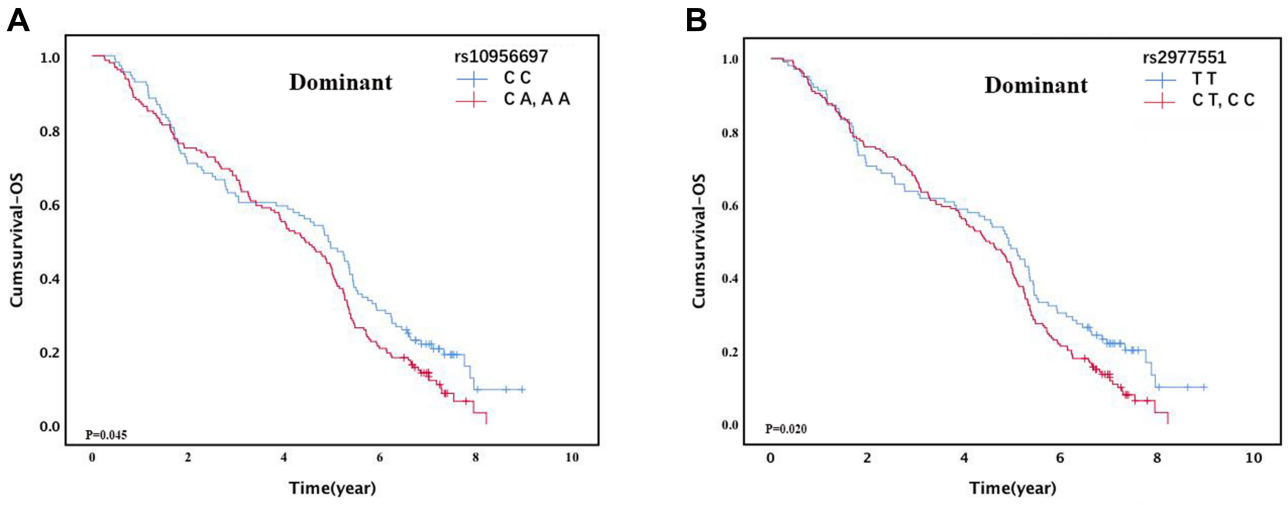

Figure 2 Kaplan–Meier plots of lung cancer patients with different genotypes of in WISP1 gene. (**A**) OS of lung cancer patients by rs10956697 using dominant model. (**B**) OS of lung cancer patients by rs2977551 using dominant model.

In conclusion, our investigation provided the useful basics to make more precise evaluation of the chemotherapy efficacy and then further design personalized therapy.

The differential expression status of WISP1 between the tumor tissue and normal healthy tissue.[9] High levels of WISP1 correlated with survival in prostate adenocarcinoma and overall survival in primary melanoma, low-grade glioma, and kidney papillary cell carcinoma.[29] WISP1 could regulate complex biological process during disease by effecting proliferation, cell survival, and cell differentiation, development and disease.[10,16,30,31] It had been pointed out that WISP1 protects lung carcinoma cells from intrinsic p53-dependent, but not extrinsic Fas ligand-activated.[32] Increased epithelial cell proliferation and EMT induction highlight WISP1 as a possible linker of organ fibrosis and cancer.[33] The correlation of its expression with clinical outcome makes WISP1 a promising target for the evaluation of clinical diagnosis and prognosis of cancers.

Table 3 Association Between Single Nucleotide Polymorphisms (SNPs) and Disease Progression in Lung Cancer Patients

Gene/SNP	Genotype	T Stage				N Stage				M Stage			
		T1/T2	T3/T4	OR (95% CI)	P	N0	N1/N2/N3	OR (95% CI)	P	M0	M1	OR (95% CI)	P
rs16904853	CC	26	102	Ref.	0.060	2	6	Ref.	0.199	13	41	Ref.	0.735
	CT/TT	28	100	0.542 (0.286–1.027)		11	187	0.587 (0.260–1.324)		43	109	1.135(0.546–2.358)	
	CC/CT	62	99	Ref.	0.858	28	133	Ref.	0.933	56	111	Ref.	0.050
	TT	14	29	0.858(0.426–1.731)		8	36	0.962(0.390–2.377)		5	38	0.386(0.150–0.999)	
rs10956697	CC	37	41	Ref.	0.216	15	73	Ref.	0.683	19	69	Ref.	0.312
	CA/AA	39	76	0.691(0.384–1.242)		21	94	1.174 (0.544–2.531)		34	81	1.414 (0.723–2.767)	
	CC/CA	67	112	Ref.	0.964	31	148	Ref.	0.700	49	130	Ref.	0.512
	AA	9	15	1.021(0.413–2.518)		5	19	1.247(0.407–3.821)		43	20	0.673(0.207–2.188)	
rs2929965	CC	26	35	Ref.	0.858	13	48	Ref.	0.779	12	49	Ref.	0.281
	CT/TT	51	89	1.122(0.318–3.956)		23	117	1.160 (0.413–3.259)		43	97	1.687 (0.652–4.366)	
	CC/ CT	65	12	Ref.	0.762	31	5	Ref.	0.843	49	6	Ref.	0.931
	TT	105	19	1.245(0.302–5.135)		139	26	0.830(0.131–5.252)		121	25	0.931(0.180–4.817)	
rs2929973	TT	41	45	Ref.	**0.015**	17	69	Ref.	0.654	17	69	Ref.	0.066
	GT/GG	36	82	0.486 (0.271–0.871)		19	100	0.841 (0.395–1.792)		39	80	1.868 (0.960–3.634)	
	TT/ GT	72	113	Ref.	0.446	32	153	Ref.	0.785	52	133	Ref.	0.539
	GG	7	14	0.673(0.243–1.865)		4	16	1.182(0.354–3.949)		4	16	0.691(0.212–2.252)	
rs7828685	AA	35	47	Ref.	0.275	14	68	Ref.	0.784	18	64	Ref.	0.153
	GA/GG	43	81	0.723 (0.404–1.294)		22	103	1.114 (0.513–2.421)		38	86	1.626 (0.834–3.170)	
	AA /GA	68	105	Ref.	0.380	30	142	Ref.	0.890	51	122	Ref.	0.190
	GG	10	22	0.692(0.304–1.573)		6	28	1.074(0.390–2.963)		5	28	0.499(0.176–1.413)	
rs2977551	TT	40	42	Ref.	**0.005**	17	65	Ref.	0.374	19	63	Ref.	0.187
	CT/CC	37	89	0.428 (0.238–0.771)		19	107	0.708 (0.330–1.517)		38	88	1.564 (0.805–3.038)	
	TT/ CT	69	109	Ref.	0.212	31	147	Ref.	0.768	52	126	Ref.	0.263
	CC	8	22	0.572 (0.238–1.375)		5	25	0.850 (0.288–2.504)		5	23	0.549 (0.192–1.569)	
rs2977549	TT	41	41	Ref.	**0.005**	18	64	Ref.	0.327	20	62	Ref.	0.376
	CT/CC	39	91	0.438 (0.246–0.781)		20	110	0.690 (0.328–1.450)		38	92	1.339 (0.701–2.558)	
	TT/ CT	70	108	Ref.	0.277	33	145	Ref.	0.746	53	125	Ref.	0.167
	CC	10	24	0.640(0.286–1.432)		5	29	0.839(0.291–2.420)		5	29	0.505(0.192–1.331)	

Notes: $P < 0.05$ are indicated in bold text; P, *P*-value for binary logistic regression analysis.
Abbreviations: OR, odds ratio; CI, confidence interval; Ref., reference.

Table 4 Stratified Analysis of the Association Between rs2929973, rs2977551, rs2977549 and Prognosis in Lung Cancer Patients

SNP	Subgroups	Overall Survival (OS)				Progression-Free Survival (PFS)			
		Death/Total		HR (95% CI)	P	Progression/Total		HR (95% CI)	P
		11	12/22			11	12/22		
rs2929973	Age (years)								
	≤60	45/62	109/120	0.650 (0.458–0.924)	**0.016**	55/90	120/148	1.535 (1.114–2.116)	**0.009**
	Smoking status								
	Never smoker	24/33	64/71	0.617(0.383–0.994)	**0.047**	31/50	69/85	1.457(0.952–2.231)	0.083
	Histology								
	NSCLC	57/70	109/117	0.693(0.501–0.959)	**0.027**	67/97	117/143	1.338(0.990–1.808)	0.058
	TNM stage								
	III/IV	59/75	107/114	0.649(0.470–0.896)	**0.009**	70/102	119/143	1.377(1.024–1.852)	**0.034**
	ED	10/10	25/27	1.002(0.466–2.156)	0.995	10/19	28/32	2.550(1.188–5.473)	**0.016**
rs2977551	Age (years)								
	≤60	26/28	130/154	1.222(0.800–1.867)	0.353	53/85	121/153	1.413(1.022–1.954)	**0.037**
	Smoking status								
	Never smoker	11/12	36/47	1.858(0.434–1.695)	0.660	27/45	71/89	1.572(1.007–2.455)	**0.047**
rs2977549	Age (years)								
	≤60	54/66	104/117	1.178(0.846–1.639)	0.332	54/84	117/145	1.480(1.071–2.047)	**0.018**
	Histology								
	NSCLC	56/68	114/122	1.502(1.087–2.075)	**0.014**	66/93	51/121	1.358(1.005–1.835)	**0.046**
	SCLC	82/100	165/182	1.288(0.987–1.682)	0.063	77/119	133/176	1.350(1.018–1.791)	**0.037**
	TNM stage								
	III/IV	55/69	115/123	1.601(1.157–2.216)	**0.005**	66/95	126/155	1.419(1.053–1.913)	**0.022**
	ED	11/11	24/26	0.765(0.362–1.615)	0.482	11/20	27/32	0.481(0.232–1.000)	0.050

Notes: *P* < 0.05 are indicated in bold text; P, *P*-value for multivariate Cox hazards regression analysis with adjustment for age, gender, and histology; 11/12/22 = wild type/heterozygote/homozygote.

Abbreviations: HR, hazard ratio; CI, confidence interval; Ref., reference; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma.

WISP1 signaling is critically involved in cell survival and growth, through regulating PI3K and Akt.[12] WISP1 led to Akt phosphorylation in epithelial and mesenchymal cells.[15,34] In our study, we found that WISP1 was related to platinum-based chemotherapy response of lung cancer.

Previous association studies that polymorphism is one of the factors that may affect prognosis, mainly focused on the mis-sense variants or coding regions of individual genes. In this study, we focused on the genetic alteration of WISP1, a total of 39 SNPs to study the prognosis effect platinum-based chemotherapy. Our study found WISP1 rs2929973 carrying G variant allele are more likely to have an increased susceptibility of lung cancer. Patients with younger age (≤60), or patients who had never smoked, NSCLC, or advanced tumor (TNM stage III/IV), it had better OS when rs2929973 carrying TT genotype. Patients who carry the rs2977551 CT or CC genotype tended to have a significantly increased risk of PFS in subgroups of younger (≤60 years old), never smokers. Patients carrying TT genotype in rs2977549 better OS in lung cancer patient with NSCLC, had TNM stage III/IV. In conclusion, the WISP1 rs2929973 T allele, rs2977551 T allele and rs2977549 T allele maybe a potential protective allele in the prognosis of lung cancer patients treated with platinum-based chemotherapy.

WISP1 is a downstream gene of the canonical Wnt-β-catenin pathway, and its mutations were reported to be associated with multiple diseases, including asthma, hypertension and spinal osteoarthritis.[13,34–36] Chen et al revealed that WISP1 was overexpressed in non-small cell lung carcinoma (NSCLC) samples compared with their normal lung tissue counterparts. Our previous studies revealed that WISP1 genetic polymorphisms were related to susceptibility and the platinum-based chemotherapy response of lung cancer, and

we hypothesized that WISP1 polymorphisms may also be associated with the chemotherapy toxicity of lung cancer.[28] Most previous studies about the relationships of WISP1 polymorphisms and diseases were focused on the polymorphisms of WISP1 rs2929973. However, results from different studies often provide contradicting results or statistically non-significant associations. Previous study indicated that WISP1 rs2929973 was associated with asthma and individuals carrying the G allele of rs2929973 conferring lower forced expiratory volume in the first second.[37] Patients carrying the WISP1 rs2929973 GG and TT variant were almost twice as likely as those carrying the GT genotype to have estrogen receptor (ER)- and progesterone receptor (PR)-positive tumors.[38] In addition, the genetic polymorphisms of WISP1 (rs2977549) variants were associated with lung and smoking-related cancer prognosis.[27] Previous research found that patient carrying the rs10956697 AC genotype had a significantly decreased risk of gastric cancer (OR = 0.58, 95% CI 0.35–0.98). Smokers with the rs10956697 AC and AC + AA genotypes exhibited a 0.28-fold lower and 0.32-fold lower risk of gastric cancer.[39] Rs16904853, rs2977549, and rs2977551 polymorphisms were significantly associated with hematologic toxicity.[27]

However, our study has several limitations. Independent validation of correlations between association of SNPs with lung cancer prognosis are needed. No SNPs remained significant by considering multiple-testing correction that calculated the p value of the SNPs by FDR-BH (Benjamini & Hochberg (1995) step-up FDR control) correction, it perhaps the sample size for the study is not large enough. Moreover, the function represent interconnections between polymorphisms and prognosis of lung cancer patients with platinum-based chemotherapy was not determined in our study.

Conclusion

In conclusion, lung cancer patients with WISP1 rs2929973 GT or GG, rs2977551 CT or CC and rs2977549 CT or CC genotypes had increased risk of disease progression, and patients with rs2977551 CC or CT had a significantly longer OS. Our results showed that those polymorphisms were significantly associated with the chemotherapy prognosis of lung cancer patients. Thus, we thought that the genotypes of WISP1 may be contributed to a potential candidate biomarker for the prediction of prognosis in lung cancer patients.

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Disclosure

The authors declare that they have no conflicts of interest.

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