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Original Article

Association of common polymorphisms in *p53* and *MDM2* with platinum-related grade III/IV toxicities in Chinese advanced lung adenocarcinoma patients

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Abstract: Lung adenocarcinoma (LAC) is a predominant form of lung cancer worldwide with a high mortality. The treatment-related toxicity is an important side effect for the patients with advanced disease after combined chemotherapy. MDM2-p53 pathway have lead role in regulation of platinum-induced DNA damage responses, and the functional polymorphisms could affect the capacity to DNA damage responses and apoptosis of normal tissue cells. Herein we investigated two common polymorphisms of p53 and MDM2 genes, rs1042522 and rs2279744, and their associations with the occurrence of grade III/IV toxicities by logistic regression models in 292 stage III and IV lung adenocarcinoma patients following the first-line with platinum-based chemotherapy. Adjusting covariates were age, sex, smoking status, performance status, TNM stage and chemotherapy regimen. Analysis of the two common polymorphisms based on three genetic models, we found that rs1042522 was not associated with incidence of severe hematologic toxicity. The results showed that rs2279744 was statistically significant risk factor for grade III/IV hematologic toxicity in additive (adjusted OR = 1.904, 95% CI = 1.149-3.156, *P* = 0.013) and recessive models (adjusted OR = 2.128, 95% CI = 1.198-3.777, P = 0.010). However, there was no statistically significant association between either the rs1042522 or rs2279744 polymorphism and grade III/IV gastrointestinal toxicity. In addition, the combined effects of rs1042522 and rs2279744 on risk of severe toxicities have not observed in present study. These results suggested that MDM2 rs2279744 might be used as a candidate biomarker for prediction of severe hematologic toxicity in advanced adenocarcinoma patients who had first-line platinum-based chemotherapy.

Keywords: Lung adenocarcinoma, p53, MDM2, hematologic toxicity, gene polymorphism, biomarker

Introduction

Lung cancer continues to be a severe global health problem and is the most commonly diagnosed malignancy worldwide, with a 5-year survival rate of less than 15% in most countries [1-3]. Of which the majority are non-small cell lung cancer (NSCLC), and nearly two-thirds of NSCLC patients are diagnosed at advanced stages, locally or more frequently disseminated [3, 4]. Lung adenocarcinoma (LAC) is a predominant form of NSCLC, accounts for more than 50% of all NSCLC and its incidence has been increasing recently [5].

Combination chemotherapy can prolong the survival of patients with advanced LAC, and the use of platinum-based combination chemotherapy is the standard treatment for advanced LAC. However, the treatment-related side effects, such as hematologic toxicity and gastrointestinal toxicity, are the ongoing and unsolved obstacles in clinically. The most commonly used platinum compounds are cisplatin and carboplatin. They cause DNA damages within cancer cells are thought to be the main therapy targets, and kill the cells mainly via DNA damage-induced apoptosis pathway [6]. A growing number of studies have indicated that numerous genetic polymorphisms of drug-transporting, drug-metabolizing and DNA repair enzyme-coding genes are associated with the clinical response outcomes and side effects of the platinum-based combination chemotherapy for human cancer treatment [7-12]. In addition, a large body of evidence indicates that MDM2-p53 pathway have crucial role in regulating platinum-induced DNA damage responses and

apoptosis [13-15]. And so the functional gene polymorphisms in this pathway could improve or weaken the efficacy and toxicity of cancer therapies [15, 16].

Previous study have shown that two common single-nucleotide polymorphisms (SNPs) of p53 and MDM2 genes, rs1042522 (p53 p. Pro-72Arg) and rs2279744 (MDM2 c.14+309T>G), could affect cancer development [17-19] and individual response and related-toxicity outcomes in cancer chemotherapy [20-24]. However, the association of the two polymorphisms with toxicity outcomes of platinum-based combination chemotherapy for lung cancer remains controversial [20, 22]. There is an urgent need to investigate two common polymorphisms for the prediction of combination chemotherapy related-toxicity for lung cancer, especially with the majority in lung adenocarcinoma, in order to be able to offer personalized chemotherapy for individual patients. In the present study, we aimed to investigate the association of the two common SNPs (rs1042522 and rs2279744) with severe chemotherapy-related toxic effects in advanced LAC patients.

Materials and methods

Patient eligibility and data collection

This study includes LAC patients admitted to the Institute of Cancer Research between August 2009 and September 2014. Only patients (292 subjects) with histologically confirmed clinical stages III to IV LAC participated in the study. All subjects were unrelated ethnic Han Chinese. Informed consent was obtained from the patients. The study protocol was approved by the ethics committees of the Jinling Hospital and Nanjing University.

Patients receiving radiation and cancer targeting therapy were excluded, and they were given at least two cycles of first-line chemotherapy in combination with 75 mg/m^2 cisplatin or carboplatin AUC 5, administered intravenously on day 1, every 3 weeks. The clinical data were systematically recorded by medical history interview, physical examination and laboratory test at the admission time, including age at diagnosis, sex, tobacco consumption, family history, routine hematology and biochemistry parameters, ECOG/WHO/Zubrod performance score (ZPS), tumor-node-metastasis (TNM) stage, and imaging characteristics (acquired by chest radiographs, computed tomography of the thorax and abdomen, and magnetic resonance imaging of brain and bone scan).

Treatment response and toxicity assessment

Patients were evaluated for response after first two cycles of chemotherapy according to the response evaluation criteria in solid tumors criteria (RECIST, version 1.1), which classify the responses into the following four categories: complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD).

Toxicity assessment of chemotherapy with platinum was based on the National Cancer Institute's Common Toxicity Criteria for Adverse Events (NCI-CTCAE) version 3.0 (http://ctep.cancer.gov) during first-line chemotherapy. The toxicities included data of leukocytopenia, anemia, thrombocytopenia, nausea, and vomiting, and were grouped into grade III/IV hematologic and gastrointestinal toxicities. Grading of toxicity was done by an investigator who was blind to the genotyping results. The study was approved by the Institutional Review Board in Jinling Hospital and complied with the Declaration of Helsinki.

DNA extraction and genotyping

Blood samples were obtained from all recruited NSCLC patients after signing informed consent forms. Genomic DNA was isolated from blood samples using the QIAamp DNA Blood Kit (Qiagen). Extracted DNA samples were aliquoted, flash frozen, and stored at -80°C until use. The genotypes of rs1042522 (p53 p. Pro72Arg) and rs2279744 (MDM2 c.14+309T>G) were determined by PCR-RFLP technique as des cribed previously [21], and followed by the direct sequencing of 15% samples with the heterozygous or homozygous variant. The direct sequencing results were all consistent with the corresponding PCR-RFLP results. Direct sequencing of the PCR product was performed with Big Dye Terminator v3.1 kit (ABI PRISM 3100 Genetic Analyzer, Applied Biosystems).

Statistical analysis

Categorical variables, expressed as percentages, were evaluated by χ^2 test or Fisher's exact

Table 1. Patient characteristics

Characteristics		n (% of patients)
Total no. of patients		292 (100)
Age at diagnosis, Median (range)	58 (37-80)	
Gender		
Male		204 (69.9)
Female		88 (30.1)
Smoking habit		
Smoker		159 (54.5)
Non-smoker		133 (45.5)
ZPS class		
0-1		282 (96.6)
2		10 (3.4)
TNM stage		
III		122 (41.8)
IV		170 (58.2)
Chemotherapy regimen		
Combined with cisplatin		230 (78.8)
Combined with carboplatin		62 (21.2)
Response		
Complete response (CR)		1 (3.4)
Partial response (PR)		56 (19.2)
Stable disease (SD)		184 (63.0)
Progressive disease (PD)		33 (11.3)
Not evaluable		18 (6.2)
Toxicity outcomes		
Grade III/IV hematologic toxicity		102 (34.9)
Grade III/IV gastrointestinal toxicity		35 (12.0)
rs1042522 (*p53* p. Pro72Arg)		
G/G		99 (33.9)
G/C		134 (45.9)
C/C		59 (20.2)
rs2279744 (*MDM2* c.14+309T>G)		
G/G		87 (29.8)
G/T		196 (67.1)
T/T		9 (3.1)

test. Bonferroni correction was used to adjust the significance level of a statistical test when multiple comparisons were been made. The associations between the genetic polymorphisms and toxicity outcomes to chemotherapy were estimated by odds ratios (OR) and their 95% confidence intervals (95% CI), which were calculated using logistic regression model. The covariates of toxicities included age at diagnosis, sex, smoking status, PS class, TNM stage and chemotherapy regimen. *P*-values were two-sided and a level of less than 0.05 was considered statistically significant. All statistical analyses were carried out using the statistical software program package SPSS for Microsoft Windows version 16.0.

Results

Two hundred and ninety-two LAC patients with stages III to IV were enrolled, and the patient characteristics shown in **Table 1**. The median age of the patients was 58 years (range 37 to 80 years), and 204 (69.9%) patients were female. There were 159 smokers and 133 non-smokers. 96.6% of the patients (282/292) showed ZPS of 1 or 0. All enrolled patients had advanced LAC (stage III or IV), with 41.8% at stage III, and 58.2% at stage IV. The most LAC patients (78.8%) were received combined with cisplatin-based chemotherapy as first-line treatment. The other 21.2% (62) patients were treated with carboplatin-based combination chemotherapy. After evaluation of the combination chemotherapy-related toxicities, grade III/IV hematologic toxicity was recorded in 102 patients (34.9%), and only 35 patients (12.0%) had grade III/IV gastrointestinal toxicity.

Of the 292 eligible patients, 18 were excluded from response outcome analysis because of missing records of the clinical response to treatment. The remaining 274 patients constitute the study sample, of whom 22.6% (57) had response to treatment (CR and PR), 74.3% (217) showed no response (SD and PD) (**Table 1**). To investigate whether the chemotherapy response was related to various patient characteristics, the patients were grouped according to sex, smoking status, ZPS class, TNM stage, chemotherapy regimen, and the genotypes of p53 and MDM2. We have not observed the significant association between chemotherapy response and basic patient characteristics (sex, smoking status, ZPS class, TNM stage, chemotherapy regimen and the genotypes of two investigated polymorphisms) in the LAC patients (**Table 2**).

Table 2. Response to chemotherapy according to patient characteristics

Variable	N	Patients with CR + PR, n (%)	*P*-value	Patients with CR + PR + SD (%)	*P*-value
All patients	292	57 (19.5)		241 (82.5)	
Eligible patients	274	57 (20.8)		241 (88.0)	
Gender					
Male	194	43 (22.2)		170 (87.6)	
Female	80	14 (17.5)	0.387	71 (88.8)	0.795
Smoking status					
Smoker	152	34 (22.4)		130 (85.5)	
Non-smoker	122	23 (18.9)	0.476	111 (91.0)	0.168
ZPS class					
0-1	266	56 (21.1)		233 (87.6)	
2	8	1 (12.5)	1.000	8 (100)	0.602
TNM stage					
IIIA	28	8 (28.6)		26 (92.9)	
IIIB	89	17 (19.1)		77 (86.5)	
IV	157	32 (20.4)	0.549	138 (87.9)	0.667
Chemotherapy					
Combined with cisplatin	212	46 (21.7)		187 (88.2)	
Combined with carboplatin	62	11 (16.7)	0.580	54 (87.1)	0.813
rs1042522 (*p53* p. Pro72Arg)					
G/G	92	18 (19.6)		81 (88.0)	
G/C	126	27 (21.4)		114 (90.5)	
C/C	56	12 (21.4)	0.938	46 (82.1)	0.280
rs2279744 (*MDM2* c.14+309T>G)					
G/G	82	16 (19.5)		71 (86.6)	
G/T	183	37 (20.2)		161 (88.0)	
T/T	9	4 (44.4)	0.205	9 (100)	0.502

Abbreviations: CR, Complete response; PR, partial response; SD, stable disease.

To investigate the associations of chemotherapy-related toxicities in various categories of patient characteristic, we performed the stratification analysis in **Table 3**. There are no significant associations of grade III/IV hematologic toxicity with patient characteristics in advanced LAC patients (**Table 3**). The grade III/IV gastrointestinal toxicity only showed significant association with smoking status for non-smokers (P = 0.028, **Table 3**). All possible covariates were adjusted before data analysis of the associations of two polymorphisms with severe toxicities following platinum-based chemotherapy treatment. We analyzed these associations in additive, dominant and recessive models, respectively. No associations were found between rs1042522 polymorphism and the chemotherapy-related toxicities for the LAC patients regardless of genetic models (**Table 4**). However, covariates analysis results showed that rs2279744 was statistically significant risk factor for grade III/IV hematologic toxicity in additive and recessive models (adjusted OR = 1.904, 95% CI = 1.149-3.156, P = 0.013 in additive model; adjusted OR = 2.128, 95% CI = 1.198-3.777, P = 0.010 in recessive model; **Table 4**). In contrast, there are no significant associations of gastrointestinal toxicity with this polymorphic locus in three genetic models (**Table 4**).

We further investigated the combined effects of two investigated SNPs on risk of treatment-related severe toxicities, and found that the rs2279744 T allele has significant associated with risk of grade III/IV hematologic toxicity for the LAC patients regardless of rs1042522 locus (**Table 5**). In other words, we found no correlation between rs1042522 polymorphism and the risk of hematologic toxicity in LAC

Table 3. Correlation between toxicity outcome and patient characteristics

Variable	No. of the patients	Grade III/IV hematologic toxicity (%)	*P*-value	Grade III/IV gastrointestinal toxicity (%)	*P*-value
All patients	292	102 (34.9)		35 (12.0)	
Eligible patients	292	102 (34.9)		35 (12.0)	
Gender					
Male	204	72 (35.3)		20 (9.8)	
Female	88	30 (34.1)	0.843	15 (17.0)	0.080
Smoking status					
Smoker	159	57 (35.8)		13 (8.2)	
Non-smoker	133	45 (33.8)	0.719	22 (16.5)	0.028*
Performance status (PS)					
0-1	282	97 (34.4)		32 (11.3)	
2	10	5 (50.0)	0.327	3 (30.0)	0.197
TNM stage					
III	122	34 (27.9)		12 (9.8)	
IV	170	68 (40.0)	0.081	23 (13.5)	0.338
Chemotherapy					
Combined with cisplatin	230	83 (36.1)		31 (13.4)	
Combined with carboplatin	62	19 (30.6)	0.425	4 (6.5)	0.131

*Significant correlation.

Table 4. Analysis of correlation between grade III/IV toxicity outcomes and the polymorphisms with logistic regression analysis

SNP genotype	N	Grade III/IV toxicity, n (%)	Additive model		Dominant model		Recessive model	
			OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Hematologic toxicity								
rs1042522 (*p53* p. Pro72Arg)								
G/G	99	38 (38.4)	0.949 (0.673-1.358)	0.763	1.151 (0.628-2.107)	0.650	0.799 (0.476-1.340)	0.396
G/C	134	42 (31.3)						
C/C	59	22 (37.3)						
rs2279744 (*MDM2* c.14+309T>G)								
G/G	87	21 (24.1)	1.904 (1.149-3.156)	0.013*	1.451 (0.366-5.745)	0.596	2.128 (1.198-3.777)	0.010*
G/T	196	77 (39.3)						
T/T	9	4 (44.4)						
Gastrointestinal toxicity								
rs1042522 (*p53* p. Pro72Arg)								
G/G	99	16 (16.2)	0.609 (0.355-1.047)	0.073	0.356 (0.103-1.232)	0.103	0.604 (0.287-1.270)	0.183
G/C	134	16 (11.9)						
C/C	59	3 (5.1)						
rs2279744 (*MDM2* c.14+309T>G)								
G/G	87	11 (12.6)	0.906 (0.452-1.815)	0.781	0.591 (0.059-5.945)	0.655	0.947 (0.435-2.065)	0.892
G/T	196	23 (11.7)						
T/T	9	1 (11.1)						

*Significant correlation. OR adjusted for gender, age, PS status, TNM stage and types of chemotherapy regimen by unconditional logistic regression.

patients. The result also showed that there is no clear correlation between the chemotherapy-related gastrointestinal toxicity and two common SNPs of p53 and MDM2 genes (**Table 5**)

Discussion

To data, the insights into the molecular pathogenesis and biologic behavior of lung cancer have led to the development of many molecular

Table 5. Combined effects of the polymorphisms on risk of grade III/IV toxicity outcomes

SNP genotype		N	Grade III/IV toxicity, n (%)	*P* value	OR	95% CI	
rs1042522	rs2279744					Lower	Upper
Hematologic toxicity							
G/G + G/C	G/G	68	16 (23.5)		1		
C/C	G/G	19	5 (26.3)	0.869	1.105	0.338	3.615
G/G + G/C	G/T + T/T	165	64 (38.8)	0.027*	2.093	1.088	4.025
C/C	G/T + T/T	40	17 (42.5)	0.032*	2.553	1.082	6.020
Gastrointestinal toxicity							
G/G + G/C	G/G	68	11 (16.2)		1		
C/C	G/G	19	0 (0)	-	-	-	-
G/G + G/C	G/T + T/T	165	21 (12.7)	0.435	0.722	0.319	1.634
C/C	G/T + T/T	40	3 (7.5)	0.299	0.483	0.122	1.906

Abbreviations: CI, confidence interval; Lower, lower limit; Upper, upper limit. *Significant correlation. OR adjusted for gender, age, PS status, TNM stage and types of chemotherapy regimen by unconditional logistic regression.

targeted agents [25]. Some of these molecular targeted agents for lung cancer have already been applied in clinical treatment as comprehensive care to advanced lung cancer [26]. Despite these advance of therapeutic strategies, the prognosis of advanced lung cancer, especially advanced NSCLC, remains poor. The combination with platinum treatment is still considered the standard first-line treatment for advanced NSCLC. The platinum compounds, cisplatin and carboplatin, kill cancer cells by the DNA damage-mediated cell cycle arrest [6]. Platinum-caused DNA damages including DNA base chemical modifications, inter- or intra-molecular cross-linking of DNA, as well as DNA double/single-strand breaks [13, 14]. Therefore, the DNA repair capacity could affect treatment efficacy and risk of side effect incidents [8, 10-12, 27]. Given that MDM2-p53 pathway is key regulator for platinum-induced DNA damage responses in human cancer cells and/or normal bystander cells [16]. In addition, the significant association of clinical responses and side effects to platinum-based combination chemotherapy with functional genetic variants of p53 and MDM2 genes have been reported in various cancer treatment [28, 29]. It is certainly that two common functional polymorphisms of p53 and MDM2 genes (rs1042522, p53 p. Pro72Arg and rs2279744, MDM2 c.14+309T>G) have also already been widely reported [20-24]. However, the association of two polymorphisms with clinical response and toxicities for chemotherapy have not reached consensus. In this study, our goal was to investigate association between the toxicities suffering from platinum-based regimens and two common polymorphisms of p53 and MDM2 genes.

p53, as the key detector and regulator for DNA damage responses, is activated by exposure to genotoxic stress, resulting in DNA repair, cell-cycle arrest as well as cell apoptosis. The SNP of rs1042522 is a common polymorphism at fourth exon in human p53 gene. It is located within the proline-rich domain of p53 at codon 72 (p53 p. Pro72Arg, rs1042522, p53 codon 72) and encodes either a proline residue (CCC) or an arginine residue (CGC). Previous studies have been suggested that there is a big difference between the two polymorphic variants (72Pro and 72Arg) of p53 p. Pro72Arg locus for the pro-apoptotic activities in human cells following exposure to genotoxic drugs [30]. It is plausible speculated that the difference of pro-apoptotic activities of two polymorphic variants (72Pro and 72Arg) following genotoxic stress have led to different susceptible to platinum-based chemotherapy regimens in bystander cells. Wang and his colleagues showed that extensive-stage small-cell lung cancer (SCLC) patients with rs1042522 C variant having higher grade III/IV neutropenia incidence than the G carriers after combination chemotherapy plus with cisplatin [22]. In addition, the significant association of p53 p. Pro72Arg with severe side effects following platinum-based chemotherapy was also observed in various cancers [12, 21, 23, 24]. In present study, no significant association were found between p53 p. Pro72Arg and hematologic or gastrointestinal toxicity in LAC patients treated with platinum-based regimens. Nevertheless, this scenario is inconsistent with our results. That could be due to functional mutations of p53, different tolerance degree for genotoxic stress, or distinct DNA damage from caused by anticancer drugs.

MDM2 is an E3 ubiquitin protein ligase that regulates p53 activity and subcellular distribution, and participates in DNA damage responses and p53-dependent cell apoptosis [16, 31]. A common functional polymorphisms, rs2279744 (MDM2 c.14+309T>G, MDM2 SNP309), is located in the p53-dependent promoter region (P2 promoter). Bond et al. suggested that rs2279744 could serves as a rate limiting factor through attenuates the p53 tumor suppressor pathway in human carcinogenesis [31]. Experimental data from in vitro studies have demonstrated that the rs2279744 G variant increases the expression levels of mRNA and protein by approving affinity of the transcriptional activator Sp1 and thereby reduce the basal p53 levels [29, 31]. Many epidemiological studies have been also suggested that the rs2279744 was associated with risk of various cancer, patient survival as well as severe treatment-related side effects [20, 31]. It was presumed that MDM2 protein level increased by enhanced binding of Sp1 binding in normal bystander cells homozygous for G allele of rs2279744, which could attenuate the p53 response to various DNA damages caused by platinum. In the present study, we observed that LAC patients homozygous for the G allele have lower hematologic toxicity rate than those of patients with either homozygous for the T allele or heterozygous genotype. The corresponding covariates analysis suggested that rs2279744 was associated with grade III/IV hematologic toxicity in additive and recessive models (adjusted OR = 1.904, 95% CI = 1.149-3.156, P = 0.013 and adjusted OR = 2.128, 95% CI = 1.198-3.777, P = 0.010, respectively). This result indicated that the T allele of MDM2 rs2279744 is independently significant risk of severe hematologic toxicity in advanced LAC patients with platinum chemotherapy. However, there has been no correlation between rs2279744 and occurrence of severe chemotherapy-related gastrointestinal toxicity in the LAC patients. This distinguish of rs2279744 with hematologic and gastrointestinal toxicity outcomes may be due to the low incidence rate of gastrointestinal toxicity, different tolerance of normal bystander cells to cell injury caused by platinum or both.

Finally, we investigate the association of 2 common polymorphisms of p53 and MDM2 (rs1042522 and rs2279744) with toxic and side effects of platinum-based chemotherapy in advanced LAC patients. Our data indicated that MDM2 rs2279744 was associated with increased risk of occurrence of severe hematologic toxicity in LAC patients treated with platinum-based regimens. The results supported that decreased basal level of MDM2 expression might be related with increased risk of chemotherapy-related side effects in LAC patients.

Disclosure of conflict of interest

None.

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