Association between *eIF3α* polymorphism and severe toxicity caused by platinum-based chemotherapy in non-small cell lung cancer patients

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Both nephrotoxicity and ototoxicity are common severe toxicities in platinum treatment, which are obstacles to successful chemotherapy in cancer patients. Large interindividual variations to platinum-based regimens are well documented. Potential biomarkers for prediction of severe platinum toxicity and response will significantly improve clinical efficacy. *eIF3α* plays a critical role in regulating activity of the DNA repair pathway and contributes to the platinum response in lung cancer patients.

WHAT THIS STUDY ADDS

- Our study identified a novel *eIF3α* mis-sense mutation which is associated with platinum-induced nephrotoxicity and ototoxicity in Chinese patients with non-small cell lung cancer (NSCLC). This may represent a new effective biomarker to pre-identify individuals with a greater risk of experiencing platinum toxicity, and provide essential insight into personalized chemotherapy for NSCLC patients.

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Keywords

eIF3α, nephrotoxicity, non-small cell lung cancer (NSCLC), ototoxicity, platinum toxicity

Received

19 October 2011

Accepted

3 July 2012

Accepted Article Published Online

13 July 2012

AIM

Platinum-induced toxicity severely impedes successful chemotherapy in lung cancer patients. The nucleotide excision repair (NER) pathway is considered as one of the major factors contributing to platinum effects. Furthermore, genetic variances of the NER pathway influence platinum toxicity. *eIF3α*, over expressed in many malignancies, is an up-stream gene of NER and could regulate its activity. The purpose of this study was to investigate whether *eIF3α* polymorphism is associated with severe platinum toxicity in patients with non-small cell lung cancer (NSCLC).

METHODS

Two hundred and eighty-two incident NSCLC patients, from three different institutions, were enrolled and followed up. These patients were diagnosed and histologically confirmed with non-small cell lung cancer. All patients accepted platinum based chemotherapy for at least two cycles. Twenty-two SNPs of *eIF3α* were detected in these patients.

RESULTS

eIF3α Arg803Lys C > T polymorphism was associated with cisplatin-induced toxicity in NSCLC patients ($P = 0.02$, OR = 0.54, 95% CI 0.32, 93). T-carrier subjects presented better tolerance to platinum nephrotoxicity, but poorer tolerance to ototoxicity.

CONCLUSION

eIF3α Arg803Lys was associated with platinum toxicity in NSCLC patients and could be considered as a predictor for pretreatment evaluation in lung cancer patients.

Introduction

Lung cancer is the leading cause of death in oncologic patients and continues to be a serious global problem [1]. In lung cancer, approximately 85% of patients are histologically diagnosed with non-small cell lung cancer (NSCLC). Most of the patients are confirmed during the advanced stages presenting with stage III or IV, due to the delay in clinical diagnosis. NSCLC, an aggressive malignant carcinoma, presents with a high growth rate, widespread metastases, poor prognosis and disappointing estimated 5 year survival rates of about 15% [2, 3]. Platinum-based chemotherapy, such as cisplatin or carboplatin in combination with gemcitabine, paclitaxel, docetaxel and etoposide, is considered as the standard first line treatment for NSCLC patients [4]. However, individual variation in agent efficacy and platinum resistance is one of the major obstacles for successful chemotherapy [5]. Furthermore, several serious side effects of platinum significantly restrict its efficient clinical application, such as nephrotoxicity, ototoxicity, neurotoxicity, haematological toxicity and gastrointestinal toxicity. These adverse effects impair the functional status of cancer patients, decrease tolerant ability for further therapies and result in many severe complications [6].

The nucleotide excision repair (NER) pathway has been suggested to be the main cellular defence mechanism against platinum-induced intrastrand cross-links in DNA repair [7]. Polymorphisms of genes involved in the NER pathway, such as the xeroderma pigmentosum group D (XPD), X-ray cross complementation (XRCC) and DNA excision repair protein (ERCC), were suggested to be associated with efficacy and toxicity of platinum treatment [8, 9]. Interindividual variation in susceptibility to platinum toxicity is a major problem for efficient therapy and pre-identification of individuals with a greater risk of experiencing platinum toxicity would significantly improve clinical efficacy for platinum treatment.

eIF3α is the largest subunit of eukaryotic translation initiation factor 3 (eIF3), known to be over-expressed in many malignancies. It has been suggested that it is an upstream gene of NER pathway, contributing to tumour genesis and platinum resistance [10–14]. Our previous study revealed that the *eIF3α* expression level was related to platinum chemosensitivity [15]. It could regulate the expression level of certain core proteins involved in the NER pathway *in vitro*. We have found two novel mis-sense mutations of *eIF3α*, Arg438Lys and Arg803Lys, in the Chinese Han population *in vivo* (submitted for publication). *eIF3α* also interacts with mammalian target of rapamycin (mTOR) pathway, which is suggested to contribute significantly to tumor progression and chemotherapy sensitivity. Certain SNPs of this pathway are also related to platinum efficacy and toxicity in lung cancer patients [16, 17]. Epidemiological investigation suggested that polymorphisms of *eIF3α* are associated with breast cancer sus-

ceptibility [18]. However, it is still unknown whether *eIF3α* genetic variances are associated with platinum toxicities in lung cancer patients. In this study, we did a retrospective analysis to evaluate the possible correlation between *eIF3α* polymorphisms and platinum-based chemotherapeutic toxicity in patients with NSCLC in the Chinese Han population.

Methods

Patients

We received clinical research permission from the Chinese Clinical Trial Registry and the Registration Number is ChiCTR-TNC-10000895. The protocol for this study was IRB approved by the Committee for Medical Ethics, Institute of Clinical Pharmacology, Central South University with a registration number of ICPXL-080015. All subjects provided written consent in compliance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) before the study began.

In total, 282 NSCLC patients were recruited into our research. In the discovery study, study I, we enrolled 104 patients from Xiangya Hospital of Central South University, Hunan province from 2006 to 2008. In the replication study, study II, 84 patients were enrolled from Zhongnan Hospital of Wuhan University, Hubei province from 2006 to 2009. During the same period of time, 94 patients were enrolled from Xijing Hospital in Shanxi Province. Clinical characteristics were systematically recorded at entry, including age at diagnosis, gender, smoking status, family history of cancer, clinical stage, tumour histology and so on. Pack-year value of smoking ((cigarettes day⁻¹/20) × smoking years) was used to categorize light and heavy smokers with the cut point of 50 percentile, which was 25 in our research.

All subjects were recruited from different locations in China and from genetically unrelated ethnic Han Chinese. The carcinoma cases were newly diagnosed with incident NSCLC. All patients had inoperable advanced stage IIIA-IV, histologically or cytologically confirmed, including squamous cell carcinoma, large cell carcinoma and adenocarcinoma. All subjects accepted platinum-based (cisplatin or carboplatin) chemotherapy for at least two cycles.

Inclusion criteria were as follows: (1) blood test (haemoglobin level ≥8 g ml⁻¹, leucocyte count ≥1.5 × 10⁹ l⁻¹, platelet count ≥100 × 10⁹ l⁻¹); (2) liver function test (alanine transaminase ≤1.5 × normal upper limit, aspartate transaminase ≤1.5 × normal upper limit); (3) kidney function test (creatinine clearance ≥60 ml min⁻¹, serum creatinine ≤1.5 × normal upper limit); (4) electrocardiography (ECG) (no cardiac arrhythmia). The exclusion criteria included: (1) previous cancer history; (2) acceptance of surgery or radiation for treating lung cancer; (3) acceptance of chemotherapy other than platinum-based drugs; (4) serious concomitant diseases (diabetes, uncontrolled

hypertension, active congestive heart failure or myocardial infarction within the last 6 months).

Chemotherapeutic treatment and toxicity identification

All patients were given first line platinum-based chemotherapy including cisplatin and carboplatin. The main chemotherapeutic regimens included cisplatin/carboplatin + gemcitabine, cisplatin/carboplatin + etoposide and cisplatin + docetaxel. There was no statistical difference in the percentage of patients treated with the same regimens when these three groups were compared. Three weeks (21 days) were considered as one cycle for all the above regimens. The chemotherapeutic protocol was as follows: cisplatin (80 mg m⁻² on day 1) plus gemcitabine (1250 mg m⁻² on day 1 and day 8); cisplatin (80 mg m⁻² on day 1) plus etoposide (80 mg m⁻² on day 1 to day 3); cisplatin (80 mg m⁻² on day 1) plus docetaxel (75 mg m⁻² on day 1 to day 3); carboplatin [area under curve (AUC) 5 on day 1] plus gemcitabine (1000 mg m⁻² on day 1 and day 8); carboplatin (AUC 5 on day 1) plus etoposide (80 mg m⁻² on day 1 to day 3). Other regimens included carboplatin, vinorelbine and cisplatin, vinorelbine and carboplatin, ifosfamide and cisplatin and irinotecan and carboplatin. All the drug names mentioned in this study conform to 'Guide to Receptors and Channels' [19]. To confirm a good chemotoxicity tolerance, all patients accepted regular tests during treatment, including routine blood tests, liver and kidney function tests, ECG and chest X-ray. After a rest period (7 days) chemotherapy was repeated. For all recruited patients, the treatment lasted for minimally two cycles and maximally six cycles. After the first two chemotherapeutic cycles, approximately 5 ml of venous blood was collected from each patient for genetic studies. Genomic DNA was extracted from whole human blood using DNeasy® Blood & Tissue Kit (QIAGEN Inc., Maryland, USA) following the standard protocols.

Toxicity was assessed according to standard National Cancer Institution Criteria 3.0 (<http://ctep.cancer.gov>). Maximum attention was paid to nephrotoxicity, neuropathy, ototoxicity, emesis, neutropenia, anaemia and thrombocytopenia. Severe toxicity or severe event consisted of grade 3 or 4 haematologic toxicity, grade 3 or 4 of emesis, grade 1–4 ototoxicity, grade 1–4 of nephrotoxicity and grade 2–3 of neuropathy. With severe haematologic toxicity, the next treatment was postponed until recovery to grade 1 or grade 0. With grade 3 and 4 gastrointestinal toxicity, the doses of each drug were reduced by 25%. With grade 2 of ototoxicity or neuropathy, platinum was discontinued. When creatinine clearance decreased to within the range of 59–41 ml min⁻¹, platinum was reduced by 25%. When creatinine clearance decreased below 40 ml min⁻¹, platinum was stopped. Clinical data were systematically recorded during treatment.

The chemotherapy response was assessed after the first two cycles of chemotherapy, using Response Evaluation Criteria in Solid Tumour Group (RECIST) guidelines

[20]. Patients with a complete response (CR) or a partial response (PR) were defined as platinum responders or platinum sensitive, and patients having stable disease (SD) or progressive disease (PD) were defined as platinum non-responders or platinum resistant. After completion of chemotherapy, these patients were followed-up.

SNP selection and sequencing

We selected 22 SNPs of the *elF3α* gene, including two novel mis-sense SNPs that we found in our previous research, Arg438Lys and Arg803Lys. Other SNPs were chosen from HapMap public SNP database. These SNPs were selected according to the following criteria: (1) minor allele frequency (MAF) of the SNP was >10% among Chinese, (2) they were SNPs associated with cancer risk or clinical outcome in a prior study, (3) they were haplotype tagger SNPs selected by Tagger program of Haploview version 4.2 (Cambridge, MA, USA) using the pair-wise tagging with default settings (pair-wise *r*² threshold 0.8) and (4) they were SNPs located in the promoter region or exon region, including non-synonymous or synonymous mutations.

In the discovery study, all 22 SNPs were detected based on restriction fragment length polymorphism, and sequencing was performed by Applied Biosystems® ABI 3730 genetic analyzer (Applied Biosystems, Foster City, USA). In the replication study, sequencing of Arg803Lys, which was found significant in discovery study, was replicated using the same method.

Statistical analysis

The Hardy–Weinberg equilibriums (HWE) of SNPs among all subjects were examined. Bonferroni correction and maximum (T) permutation were performed to compare allele frequency between moderate events and severe events. Since we tested 22 SNPs in our study, 22 times multiple comparison tests have been done during the Bonferroni correction. Genotypic test with 2 d.f. or Fisher's exact test with 2 d.f., together with the Cochran–Armitage trend test were used to analyze the association between genotypes and toxicity variance. All these analyses were performed in PLINK version 1.07 (Cambridge, MA, USA). Logistic regression was used to illustrate the potential effect of covariates on chemotherapeutic response. Age, gender, smoking status, family cancer history, stage and histological type were considered as covariates, and unconditional logistic regression was conducted to verify the adjusted odd ratio (OR) and 95% confidence intervals (95% CI). The aforementioned statistical tests were performed in SPSS 15.0 (SPSS Inc., Chicago, USA).

Result

Patient characteristics

In total, 282 NSCLC patients were enrolled, who were comprised of 192 (68.09%) males and 90 (31.91%) females. The

Table 1

Basic clinical characteristics of lung cancer patients for platinum-based chemotherapeutic treatment

Characteristics	Study I Cases (Changsha) n = 104		Study II Cases (Wuhan) n = 84		Cases (Xi'an) n = 94	
	n	%	n	%	n	%
Age (years)						
>60	37	35.58	25	29.76	29	30.85
60–50	42	40.38	32	38.10	32	34.04
≤50	25	24.04	27	32.14	33	35.11
Gender						
Male	69	66.35	56	66.67	67	71.28
Female	35	33.65	28	33.33	27	28.72
Smoking status						
Yes	64	61.54	57	67.86	60	63.83
No	40	38.46	27	32.14	34	36.17
Pack-years smoked						
≤25	26	25.00	28	33.33	33	35.11
>25	38	36.54	29	34.52	27	28.72
Family history of cancer						
Yes	104	100.00	83	98.81	93	98.94
No	0	0.00	1	1.19	1	1.06
Stage						
IIIA	39	37.50	34	40.48	29	30.85
IIIB	33	31.73	27	32.14	39	41.49
IV	32	30.77	23	27.38	26	27.66
*Chemotherapeutic regimens						
Cisplatin-based chemotherapy	70	67.31	63	75.00	71	75.53
Carboplatin-based chemotherapy	34	32.69	21	25.00	23	24.47

*Cisplatin-based chemotherapy: cisplatin + gemcitabine, cisplatin + etoposide, cisplatin + docetaxel, vinorelbine + cisplatin, ifosfamide + cisplatin and so on. Carboplatin-based chemotherapy: carboplatin + gemcitabine doublets, carboplatin + etoposide, vinorelbine + carboplatin, irinotecan + carboplatin and so on.

age of all patients ranged from 34 to 76 years with median of 56 years. Fifty percent of the pack-year value in our study was 25, according to which, of the patients who smoked (64.18%, $n = 181$), 30.85% ($n = 87$) were light smokers and 33.33% ($n = 94$) were heavy smokers. Only two patients (0.71%) had family history of cancer. Most patients ($n = 224$, 79.43%) had a good performance status (0–1). All patients had advanced inoperable and histological advanced NSCLC, 102 (36.17%) in stage IIIA, 99 (35.11%) in stage IIIB and 81 (28.72%) in stage IV. All accepted platinum-based chemotherapy initially for at least two cycles.

Two hundred and four (72.34%) patients received cisplatin-based chemotherapy, including cisplatin + gemcitabine, cisplatin + etoposide doublets, cisplatin + docetaxel doublets, vinorelbine and cisplatin, ifosfamide and cisplatin and so on. The other 78 (27.66%) patients received carboplatin-based chemotherapy, including carboplatin + gemcitabine doublets, carboplatin + etoposide, vinorelbine + carboplatin, irinotecan + carboplatin and so on. All basic clinical characteristics are shown in Table 1.

elF3α polymorphism and platinum toxicity

Platinum toxicity was divided into two categories: moderate toxicity (moderate events) and severe toxicity (severe

events) according to the National Cancer Institute as well as clinical chemotherapeutic guideline. Patients were classified as having good or poor tolerance (Table 2). Severe haematologic toxicity referred to grade 3 or 4 neutropenia ($n = 103$, 36.52%), grade 3 or 4 anaemia ($n = 100$, 35.46%) or grade 3 or 4 thrombocytopenia ($n = 43$, 15.25%). Grade 3 or 4 emesis ($n = 54$, 19.15%) was defined as intolerant gastrointestinal toxicity. One hundred and forty-two patients (50.35%) suffered ototoxicity with grade 1 to 4. One hundred and sixty-one subjects (57.09%) had severe nephrotoxicity (Grade 1 to 4). Intolerant neuropathy, grade 2 to 3, occurred in 111 patients (39.69%).

In the discovery study, the Arg803Lys polymorphism was associated with intolerant nephrotoxicity. Logistic regression showed that T-carriers had 0.34 fold better tolerance (95% CI 0.13, 0.89) compared with CC homozygotes, after adjustment for gender, age, smoking status, cancer stage, family history and chemotherapy regimens. In the replication study, relationship between Arg803Lys and nephrotoxicity could not be reproduced. However, we found this mutation was also related to severe ototoxicity in one cohort in the replication study. There were significant differences between alleles ($P = 0.01$) as well as between genotypes ($P = 0.01$) as shown in Table 3. Permutation procedure established empirical $P_{perm} = 0.01$ and the

Table 2

Groups of graded platinum toxicities in lung cancer patients

Side effect	Grade of toxicity considered as moderate event	Grade of toxicity considered as severe event
Study I Changsha (n = 104)		
Neutropenia	0–2 (70, 67.31%)*	3–4 (34, 32.69%)
Anaemia	0–2 (67, 64.42%)	3–4 (37, 35.58%)
Thrombocytopenia	0–2 (86, 82.69%)	3–4 (18, 17.31%)
Emesis	0–2 (85, 81.73%)	3–4 (19, 18.27%)
Ototoxicity	0 (56, 53.85%)	1–4 (48, 46.15%)
Nephrotoxicity	0 (41, 39.42%)	1–4 (63, 60.58%)
Neuropathy	0–1 (58, 55.77%)	2–3 (46, 44.23%)
Study II Wuhan (n = 84)		
Neutropenia	0–2 (53, 63.10%)	3–4 (31, 36.90%)
Anaemia	0–2 (60, 71.43%)	3–4 (24, 28.57%)
Thrombocytopenia	0–2 (71, 84.52%)	3–4 (13, 15.48%)
Emesis	0–2 (74, 88.10%)	3–4 (10, 11.90%)
Ototoxicity	0 (36, 42.86%)	1–4 (48, 57.14%)
Nephrotoxicity	0 (39, 46.43%)	1–4 (45, 53.57%)
Neuropathy	0–1 (51, 60.71%)	2–3 (33, 39.29%)
Study II Xi'an (n = 94)		
Neutropenia	0–2 (56, 59.57%)	3–4 (38, 40.43%)
Anaemia	0–2 (55, 58.51%)	3–4 (39, 41.49%)
Thrombocytopenia	0–2 (82, 87.23%)	3–4 (12, 12.77%)
Emesis	0–2 (69, 73.40%)	3–4 (25, 26.60%)
Ototoxicity	0 (48, 51.06%)	1–4 (46, 48.94%)
Nephrotoxicity	0 (41, 43.62%)	1–4 (53, 56.38%)
Neuropathy	0–1 (62, 66.96%)	2–3 (32, 34.04%)
Total (n = 282)		
Neutropenia	0–2 (179, 63.48%)	3–4 (103, 36.52%)
Anaemia	0–2 (182, 64.54%)	3–4 (100, 35.46%)
Thrombocytopenia	0–2 (239, 84.75%)	3–4 (43, 15.25%)
Emesis	0–2 (228, 80.85%)	3–4 (54, 19.15%)
Ototoxicity	0 (140, 49.65%)	1–4 (142, 50.35%)
Nephrotoxicity	0 (121, 42.91%)	1–4 (161, 57.09%)
Neuropathy	0–1 (171, 60.64%)	2–3 (111, 39.36%)

*Number of patients and percentage of total subjects.

Table 3

The allele and genotype frequency of *eIF3a* Arg803Lys among non-small cell lung cancer patients and the relationship with platinum-induced toxicities

	Minor allele (T)		Moderate		P†	P _{perm} ‡	T-carrier*		Moderate	P§	P _{trend} ¶	P _{adjust} **	OR (95% CI)
	Severe	Moderate					Severe	Moderate					
Study1 (n = 104)													
Ototoxicity	11 (5.29%)	18 (8.65%)	0.34	0.25			11 (10.58%)	18 (17.31%)	0.38	0.30	0.11		0.44 (0.17, 1.19)
Nephrotoxicity	13 (6.25%)	16 (7.69%)	0.06	0.05			13 (12.50%)	16 (15.38%)	0.05	0.04	0.03		0.34 (0.13, 0.89)
Study2 (n = 84)													
Ototoxicity	13 (7.74%)	12 (7.14%)	0.57	0.75			12 (14.29%)	12 (14.29%)	0.46	0.56	0.33		0.62 (0.24, 1.61)
Nephrotoxicity	9 (5.36%)	16 (9.52%)	0.05	0.05			9 (10.71%)	15 (17.86%)	0.11	0.05	0.05		0.35 (0.12, 0.98)
Study2 (n = 94)													
Ototoxicity	18 (9.57%)	6 (3.19%)	0.01	0.01			17 (18.09%)	6 (6.38%)	0.01	0.00	0.01		4.41 (1.51, 12.85)
Nephrotoxicity	13 (6.91%)	11 (5.85%)	0.81	0.58			12 (12.77%)	11 (11.70%)	0.79	0.81	0.91		0.95 (0.38, 2.36)
Overall (n = 282)													
Ototoxicity	42 (14.89%)	36 (12.77%)	0.51	0.67			40 (14.18%)	36 (12.77%)	0.58	0.48	0.71		1.11 (0.65, 1.90)
Nephrotoxicity	35 (12.41%)	43 (15.25%)	0.02	0.01			34 (12.06%)	42 (14.89%)	0.02	0.01	0.03		0.54 (0.32, 0.93)

* T-carriers included patients with TT genotype or CT genotype. †P_{value} comparing allele frequencies adjusted by Bonferroni correction. ‡P_{perm} after maximum (T) permutation. §P value comparing genotype frequencies in moderate and severe toxicity groups using genotypic test with 2 d.f. or Fisher's exact test with 2 d.f. ¶P_{trend} Cochran–Armitage trend test.

**P_{adjust} adjusted for age, gender, pack-year smoking, family history of cancer, stage and treatment in logistic regression.

Figure 1

Association between *elF3α* Arg803Lys C>T polymorphism and platinum-induced toxicity in NSCLC patients * $P=0.01$ Bonferroni correction comparing Arg803Lys allele frequencies of the severe nephrotoxicity group and the moderate nephrotoxicity group in NSCLC patients who accepted cisplatin-based chemotherapy (T-carriers include patients with TT genotype or CT genotype). ■, T-carrier; ■, CC

Cochran–Armitage test produced $P_{trend}=0.01$. After adjustment with the above-mentioned potential influences, logistic regression presented $P_{adjust}=0.01$, with an odds ratio (OR) of 4.41 for T-carriers (95% CI 1.51, 12.85). Overall, the Arg803Lys T allele is likely to be associated with severe nephrotoxicity. For allele analysis, Bonferroni correction and maximum (T) permutation showed $P=0.02$ and $P_{perm}=0.01$. For genotype analysis, T-carrier patients had a better nephrotoxicity tolerance, with $P=0.02$, $P_{trend}=0.01$ and $P_{adjust}=0.03$ (95% CI 0.32, 0.93). With regard to different chemotherapy regimens, the result was significant in NSCLC patients who received cisplatin-based chemotherapy ($P=0.01$, Figure 1), when comparing different genotypes, but no statistical difference was detected in patients with different genotypes, who received carboplatin based treatment (Figure 1).

Discussion

In this study, we investigated the role of *elF3α* polymorphisms in relation to severe platinum toxicity in patients with NSCLC. Our results showed that the Arg803Lys mutation was associated with nephrotoxicity and ototoxicity (Table 3). Identification of individuals at risk of severe platinum-induced toxicity will lead to progress in personal chemotherapeutic treatment and agent efficacy.

Symptoms of ototoxicity include subjective hearing loss, ear pain or tinnitus. Cisplatin induced hearing loss is usually irreversible and bilateral. It has been reported that there was elevation of hearing threshold in 75–100%

patients [21]. After chemotherapy, cisplatin accumulates in the cochlear tissues and induces DNA adduct formation, which could intervene in the synthesis of functional proteins and decrease the efficacy of gene translation [22]. In general, the NER pathway is considered as the main cellular defence mechanism against platinum-induced intrastrand cross-links [23]. a pharmacogenetic study showed that Lys939Gln of xeroderma pigmentosum complementation group C (XPC), a core protein in NER pathway, was associated with this adverse effect [24]. Our previous studies found that *elF3α* could interact with XPA, XPC and regulate the activation of the NER pathway. The expression levels of XPA and XPC increased after knockdown of *elF3α* in a H1299 cell line, while over-expression of *elF3α* could down-regulate the expression level of both proteins in a NIH3T3 cell line [25]. *elF3α* Arg803Lys polymorphism, located in exon 16, causes amino acid change. This missense mutation may influence the interaction with the NER pathway, and therefore contributes to synthesis of XPA and XPC protein. However, this relationship was only found in one part of study II in 94 NSCLC patients and has not been verified in all subjects. Larger prospective studies are needed to provide much more statistical power and further validation of this mutation.

Another major side effect of platinum chemotherapy is nephrotoxicity, including acute kidney injury on some patients. The prevalence of cisplatin-induced nephrotoxicity is high and occurs in at least one-third of patients [26]. Cisplatin preferentially accumulates in the kidney and the kidney is also the major route for its excretion [27, 28]. Cisplatin-induced nephrotoxicity is partially mediated by

mitogen-activated protein kinase (MAPK) pathway [29]. *eIF3α* was also suggested to contribute to transcriptional regulation of the MAPK pathway [30]. The mTOR pathway is also associated with platinum [31]. A previous study showed that mTOR interacted with the *eIF3* complex directly and activated its down-stream targets, resulting in stimulation of translation [32]. The genetic variation in the mTOR pathway was associated with platinum-induced toxicity in lung cancer patients [17]. Meanwhile, the DNA repair pathway is considered as one of the major reasons related to platinum effects [10–14]. It has also been suggested that suboptimal DNA repair, caused by the NER pathway, may lead to removal of deleterious DNA lesions in normal bystander cells, and thus impact on the toxicity with platinum chemotherapy [33]. *eIF3α*, as an up-stream gene of the NER pathway, may also contribute to platinum-induced toxicity. In our study, we found that T allele carriers of *eIF3α* Arg803Lys had a better tolerance of platinum-induced nephrotoxicity (Table 3). *eIF3α* is considered as a highly conserved gene and has high homology among different species. This mis-sense mutation, Arg803Lys, may result in essential changes of its structure and function. However, there was no significant difference between Arg803Lys polymorphism and nephrotoxicity susceptibility in carboplatin-based chemotherapy patients (Figure 1). This was possibly because carboplatin is a second generation anti-cancer drug of platinum and the nephrotoxicity occurs less frequently compared with cisplatin chemotherapy.

This study has several limitations. All patients were treated with platinum, but they also received other chemotherapeutic drugs. This may have affected the statistical results. Although we adjusted for all the potential factors, it will be much better if we could enrol cancer patients treated with exactly the same regimens in future. Furthermore, multi-cohort based larger epidemiological studies are needed to obtain more powerful results and to provide further validation for our findings.

In summary, we found that the T allele of *eIF3α* Arg803Lys polymorphism presented a better tolerance to nephrotoxicity but poorer tolerance to ototoxicity in NSCLC patients, who received platinum-based chemotherapy. Our results suggest that the *eIF3α* polymorphism could be considered as a predictive tool for toxicity evaluation of cisplatin-based chemotherapy.

Competing Interests

The authors declare no conflicts of interest.

This work was supported by the National High-Tech R&D Program of China (863 Programme) (2012AA02A517), the National Natural Science Foundation of China (81173129), the Programme for Changjiang Scholars and Innovative Research Team in University of Ministry of Education of China (IRT0946), the Special Scientific Research Foundation of

Doctor Disciplines in University of Ministry of Education of China (20110162110034) and the Natural Science Innovation Group Foundation of Hunan Province (12JJ7006).

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