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Effects of polymorphisms in the *XRCC1*, *XRCC3*, and *XPG* genes on clinical outcomes of platinum-based chemotherapy for treatment of non-small cell lung cancer

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ABSTRACT. This study aimed to investigate the effects of single-nucleotide polymorphisms (SNPs) *XRCC1* Arg194Trp, *XRCC1* Arg280His, *XRCC1* Arg399Gln, *XRCC3* Thr241Met, *XPG* His104Asp, and *XPG* His46His in genes involved in the DNA-repair pathway on the outcomes of platinum-based chemotherapy in patients with advanced non-small cell lung cancer (NSCLC). The study period was from January 2005 to January 2006, and 378 NSCLC patients were enrolled within 1 month after being diagnosed with NSCLC. Genomic DNA was extracted using the Qiagen Blood Kit. Polymerase chain reaction combined with a restriction fragment length polymorphism assay was used for genotyping. Individuals with the *XRCC1* 399A/A genotype had a higher probability of responding well to platinum-based chemotherapy, indicated by an odds ratio (OR) of

2.27 [95% confidence interval (CI) = 1.64-6.97]. Similarly, the *XPG* T/T genotype was significantly associated with improved responses to chemotherapy, indicated by an OR of 1.90 (95%CI = 1.10-3.28). The *XRCC1* 399A/A genotype was significantly associated with longer disease-free survival and overall survival, indicated by hazard ratios (HRs) of 0.48 (95%CI = 0.25-0.88) and 0.51 (95%CI = 0.26-0.98), respectively. Moreover, the *XPG* 46T/T genotype increased the likelihood of longer disease-free survival and overall survival of NSCLC patients treated with platinum-based chemotherapy (HR = 0.47; 95%CI = 0.22-0.82 and HR = 0.52; 95%CI = 0.31-0.96, respectively). These results indicate that *XRCC1* Arg399Gln and *XPG* His46His might significantly affect the clinical outcomes of platinum-based chemotherapy, highlighting the need for larger studies to confirm the role of these two SNPs in outcomes of NSCLC treatments.

Key words: SNPs; *XRCC1*; *XRCC3*; *XPG*; NSCLC

INTRODUCTION

Lung cancer is the leading cause of cancer-related deaths worldwide (IARC, 2008). Non-small cell lung cancer (NSCLC) represents almost 80% of lung cancer, of which approximately >70% present as locally advanced or metastatic cancer at the time of diagnosis because of the asymptomatic nature of early-stage NSCLC and lack of effective screening modalities (William et al., 2009).

Advanced NSCLC patients have a poor prognosis and few effective treatment options are available for these patients. Since curative surgery is not an effective treatment for NSCLC, chemotherapy has become the intervention of choice to treat advanced NSCLC. Platinum-based doublet chemotherapy is presently the standard first-line treatment for advanced-NSCLC patients. However, the response rate to platinum-based regimens of advanced NSCLC is only about 20%, with a median survival of about 7-9 months (Grønberg et al., 2009; Tahara et al., 2009). Therefore, because chemotherapy of NSCLC patients does not always effectively control tumor growth and often impairs the quality of life of patients, it is desirable to be able to efficiently select only those patients who are expected to have better responses to chemotherapy to improve the overall efficacy of chemotherapy in advanced NSCLC.

The efficiency of the DNA damage-repair system in cells is considered to be one of the most important mechanisms affecting inter-individual differences in response to chemotherapy and its clinical outcomes in patients. DNA damage induced by platinum agents is repaired predominantly by nucleotide-excision repair (NER), base-excision repair pathways (BER), and double-strand break repair. However, NER is the main pathway for repairing platinum-DNA adducts and involves the coordinated activity of >20 enzymes that remove and restore a region of DNA that contains bulky adducts (Reed, 1998; de Boer and Hoeijmakers, 2000). X-ray repair cross-complementing protein 1 (XRCC1) and X-ray repair cross-complementing protein 3 (XRCC3) are involved in BER and single-strand

break repair, which may play an important role in resistance to a variety of DNA-damaging agents. Three single-nucleotide polymorphisms (SNPs) in the *XRCC1* gene include nucleotide substitution of C to T (Arg194Trp), G to A (Arg280His), and A to G (Arg399Gln); *XRCC3* (Thr241Met) may be associated with suboptimal DNA repair systems in patients with NSCLC (Lunn et al., 1999; Weaver et al., 2005). Excision repair cross-complementing protein 5 (XPG) is another important component of NER, and nucleotide substitutions of G to A (His104Asp) and C to T (His46His) in the *XPG* gene are associated with a significantly decreased risk of lung cancer (Cheng et al., 2000; Jeon et al., 2003).

In this study, we prospectively determined the genotypes of *XRCC1* Arg194Trp, *XRCC1* Arg280His, *XRCC1* Arg399Gln, *XRCC3* Thr241Met, *XPG* His104Asp, and *XPG* His46His gene polymorphisms involved in the DNA-repair pathway and investigated the role of these SNPs in clinical outcomes of platinum-based chemotherapy in advanced NSCLC patients.

MATERIAL AND METHODS

Patients

From January 2005 to January 2006, within 1 month of being newly diagnosed with primary NSCLC, 378 patients were asked to participate in this study. All subjects were recruited mainly from the Beijing Chest Hospital and Tuberculosis and Thoracic Tumour Research Institute. Subjects who had a prior history of malignancy; an already cured tumor; or previously undergone chemotherapy, radiotherapy, or surgery were excluded from this study. Socio-demographic and clinical characteristics were included, including smoking, family history of cancer, clinical stage, and histology.

This study was approved by the Beijing Chest Hospital and Tuberculosis and Thoracic Tumour Research Institute.

Chemotherapy treatment

Patients received platinum-based doublet therapy administered as cisplatin (75 mg/m^2) on the 1st day and gemcitabine (1250 mg/m^2) on the 1st and 8th days, docetaxel (75 mg/m^2) on the 1st day, vinorelbine (25 mg/m^2) on the 1st and 8th days, or paclitaxel (150 mg/m^2) on the 1st day. The treatments were repeated every 3 weeks for a maximum of 6 cycles. If patients presented progressive disease or experienced unacceptable toxicity, the treatments were stopped. If patients showed grade 3 non-hematology toxicity and grade 4 hematology toxicity, febrile neutropenia or infection and/or thrombocytopenia associated with bleeding, doses of the cytotoxic agents in the next cycle were reduced by 25%. Patients were subsequently grouped as good responders (showing complete and partial response) or poor responders (stable and progressive disease).

Follow-up

All patients were followed up every 2 months until death or the end of the study period. The overall survival was taken as the end point. Survival time was calculated from the

date of diagnosis to the date of last follow-up or death from any causes. All the patients were followed up by telephone until November 2011.

Genotyping

All participants provided 5 mL blood, which was stored at -20°C. Genomic DNA was extracted using the Qiagen Blood Kit (Qiagen, Chastworth, CA, USA) according to the manufacturer protocol. Polymerase chain reaction (PCR) combined with a restriction fragment length polymorphism assay was used for genotyping. The *XRCC1* Arg194Trp, *XRCC1* Arg280His, *XRCC1* Arg399Gln, *XRCC3* Thr280Met, *XPG* His104Asp, and *XPG* His46His polymorphisms have been identified in previous studies (Kalikaki et al., 2009). The primers used for *XRCC1* Arg194Trp, *XRCC1* Arg280His, *XRCC1* Arg399Gln, *XRCC3* Thr241Met, *XPG* His104Asp, and *XPG* His46His are available upon request. The PCR thermal cycling conditions included initial denaturation at 95°C for 5 min, followed by 35 cycles of 94°C for 30 s, 58.5°C for 25 s, and 72°C for 30 s; a final extension was performed at 72°C for 5 min.

Statistical analysis

Demographic and clinical variables were compared across genotypes using chi-square testing. Associations of polymorphism genotypes with response to chemotherapy were tested by odds ratios (OR) and their 95% confidence interval (CI). Our primary end point was overall survival (OS) calculated as the time from diagnosis until death from any cause or last known date alive. Disease-free survival (DFS) following treatment was calculated from the initiation of therapy to first recorded date of progression, death, or last follow-up evaluation. Survival curves were constructed using the Kaplan-Meier method, and the log-rank test was used to compare patients' survival times between genotype groups. The association between the 6 SNPs and OS and DFS of NSCLC was estimated by Cox's proportional hazard model, where the most frequent genotype was used as the reference group. All analyses were performed with the SPSS Version 16.0 software (SPSS Inc., Chicago, IL, USA). Statistical significance was tested in two-sided models and defined as $P < 0.05$.

RESULTS

Patients

Table 1 shows the clinical characteristics of the pathology of the 378 patients in our study. All 378 NSCLC patients received platinum-based chemotherapy as first-line treatment, and 226 patients died during the follow-up period. The median age of patients was 62.4 ± 6.5 years and ranged from 36 to 78 years, and 298 (78.6%) of the patients were males. Older patients were at greater risk of dying from NSCLC. The majority of the patients (72.5%) were at the clinical disease stage of III to IV, and patients with NSCLC of higher clinical stages had a higher risk of death from lung cancer than those with lower NSCLC clinical stage ($P < 0.05$). Patients with the histological type of adenocarcinoma, carcinoma, or others were 216 (57.1%), 125 (33.1%) and 37 (9.8%), respectively. There were 212 patients who had a history of smoking (56.1%), and 31 (8.2%) patients had family history of cancer in first-degree relatives.

Table 1. Characteristics of the patients.

Variables	N = 378	%	Events	%	P value
Mean age (years)					
<50	24	6.4	11	4.8	
50-70	232	61.5	129	56.9	
>70	121	32.1	87	38.3	0.26
Gender					
Male	297	78.6	175	77.4	
Female	81	21.4	51	22.6	0.74
Histology					
Adenocarcinoma	216	57.1	125	55.4	
Squamous-cell carcinoma	125	33.1	79	34.8	
Other	37	9.8	22	9.8	0.89
Clinical stage					
I-II	104	27.5	41	18.1	
III	126	33.3	81	35.7	
IV	148	39.2	104	46.2	<0.05
Smoking status					
Never	166	43.9	98	43.2	
Ever	212	56.1	128	56.8	0.89
Pack-year, median					
<40	156	41.3	96	42.5	
≥40	222	58.7	130	57.5	0.77
Family history of cancer					
No	347	91.8	205	90.5	
Yes	31	8.2	21	9.5	0.65

Among the 378 patients, platinum-based chemotherapy resulted in good responses in 144 (38.1%) and in poor responses in 234 patients (Table 2). Our analysis detected a significant effect of *XRCC1* Arg399Gln and *XPG* His46His polymorphisms on responses to platinum-based chemotherapy ($P < 0.05$): individuals with the *XRCC1* 399A/A genotype were more likely to have a good response to chemotherapy, with an OR of 2.27 (95%CI = 1.64-6.97); similarly, individuals with the *XPG* T/T genotype showed a significantly better response to platinum-based chemotherapy (OR = 1.90; 95%CI = 1.10-3.28). However, we did not find any association of *XRCC1* Arg194Trp, *XRCC1* Arg280His, *XRCC3* Thr241Met, or *XPG* His104Asp with responses to chemotherapy.

Table 2. Distribution of polymorphisms in six SNPs and response to platinum-based chemotherapy.

Genotypes	Total		Good response		Poor response		OR (95%CI)
	N = 378	%	N = 144	%	N = 234	%	
XRCC1 Arg194Trp							
C/C	205	54.2	71	49.2	134	57.3	-
C/T	119	31.5	48	33.2	71	30.5	1.28 (0.78-2.09)
T/T	54	14.3	25	17.6	29	12.3	1.63 (0.84-3.12)
XRCC1 Arg280His							
G/G	232	61.5	88	61.1	144	61.7	-
G/A	131	34.6	50	34.8	81	34.5	1.01 (0.63-1.61)
A/A	15	3.9	6	4.1	9	3.8	1.10 (0.31-3.57)
XRCC1 Arg399Gln							
G/G	171	45.2	52	36.3	119	50.7	-
G/A	160	42.3	64	44.1	96	41.2	1.53 (0.94-2.57)
A/A	47	12.5	28	19.6	19	8.1	2.27 (1.64-6.97)
XRCC3 Thr241Met							
C/C	184	48.7	64	44.2	120	51.5	-
C/T	158	41.7	63	43.5	95	40.6	1.24 (0.78-1.98)
T/T	36	9.6	18	12.3	19	7.9	1.78 (0.81-3.85)
XPG His46His							
C/C	142	37.6	45	31.5	97	41.4	-
C/T	128	33.9	48	33.6	80	34.1	1.29 (0.76-2.21)
T/T	108	28.5	50	34.9	57	24.6	1.90 (1.10-3.28)
XPG His104Asp							
C/C	139	36.8	49	34.3	90	38.3	-
C/G	165	43.7	63	43.8	102	43.6	1.13 (0.69-1.86)
G/G	74	19.5	32	21.9	42	18.0	1.40 (0.75-2.59)

A multivariate analysis was performed to test for an association between the 6 SNPs and DFS and OS of NSCLC (Table 3). The *XRCC1* 399A/A genotype was significantly associated with longer DFS and OS (Figure 1) with hazard ratios (HRs) (95%CI) of 0.48 (0.25-0.88) and 0.51 (0.26-0.98), respectively. Moreover, the *XPG* 46T/T genotype was more likely to increase the DFS and OS among NSCLC patients receiving platinum-based chemotherapy (Figure 2) with HRs of 0.47 (95%CI = 0.22-0.82) and 0.52 (95%CI = 0.31-0.96), respectively. On the other hand, *XRCC1* Arg194Trp, *XRCC1* Arg280His, *XRCC3* Thr241Met, and *XPG* His104Asp did not have any detectable effects on the prognosis of NSCLC patients.

Table 3. Association of six SNPs with disease-free survival and overall survival.

	Disease-free survival				Overall survival			
	Events (N = 271)	%	HR (95%CI)	P	Events (N = 226)	%	HR (95%CI)	P value
XRCC1 Arg194Trp								
C/C	154	56.8	-		130	57.5	-	
C/T	85	31.4	0.95 (0.66-1.37)	0.77	68	30.1	0.91 (0.61-1.33)	0.58
T/T	32	11.8	0.79 (0.47-1.31)	0.34	28	12.4	0.82 (0.47-1.39)	0.43
XRCC1 Arg280His					0			
G/G	170	62.8	-		140	62.1	-	
G/A	93	34.3	0.97 (0.67-1.37)	0.85	78	34.4	0.99 (0.68-1.42)	0.94
A/A	8	2.9	0.73 (0.26-1.88)	0.48	8	3.5	0.88 (0.32-2.29)	0.78
XRCC1 Arg399Gln					0			
G/G	143	52.7	-		116	51.2	-	
G/A	109	40.2	0.81 (0.58-1.15)	0.22	94	41.4	0.87 (0.60-1.24)	0.41
A/A	19	7.1	0.48 (0.25-0.88)	<0.05	17	7.4	0.51 (0.26-0.98)	<0.05
XRCC3 Thr241Met					0			
C/C	139	51.3	-		114	50.6	-	
C/T	110	40.6	0.92 (0.65-1.30)	0.63	91	40.3	0.93 (0.65-1.34)	0.58
T/T	22	8.1	0.81 (0.43-1.49)	0.47	21	9.1	0.94 (0.50-1.75)	0.84
XPG His46His					0			
C/C	119	43.8	-		95	42.2	-	
C/T	91	33.7	0.85 (0.58-1.24)	0.37	75	33.1	0.88 (0.58-1.31)	0.21
T/T	61	22.5	0.47 (0.22-0.82)	<0.05	56	24.7	0.52 (0.31-0.96)	<0.05
XPG His104Asp					0			
C/C	107	39.5	-		87	38.5	-	
C/G	117	43.2	0.92 (0.64-1.32)	0.64	97	42.9	0.94 (0.64-1.38)	0.73
G/G	47	17.3	0.83 (0.52-1.32)	0.35	42	18.6	0.90 (0.55-1.47)	0.67

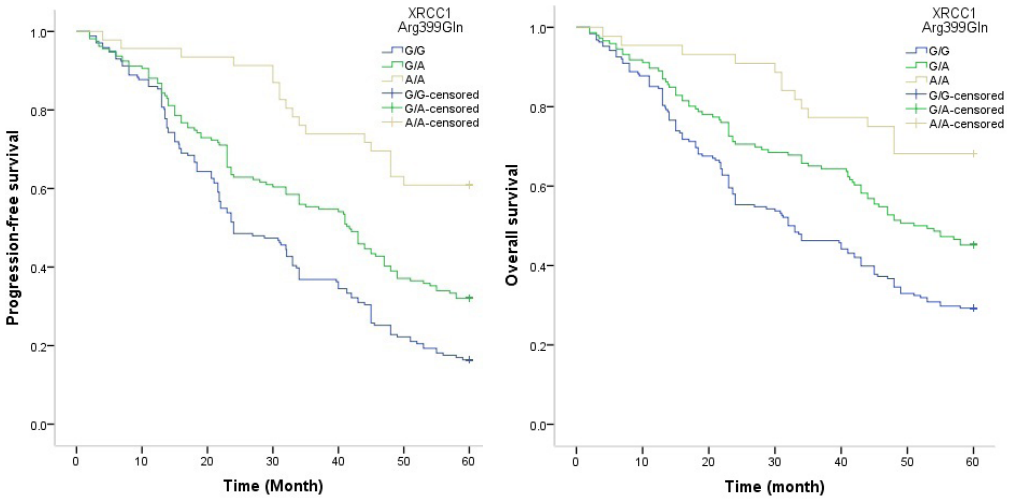

Figure 1. Kaplan-Meier estimates of disease-free survival and overall survival with the *XRCC1* Arg399Gln polymorphism.

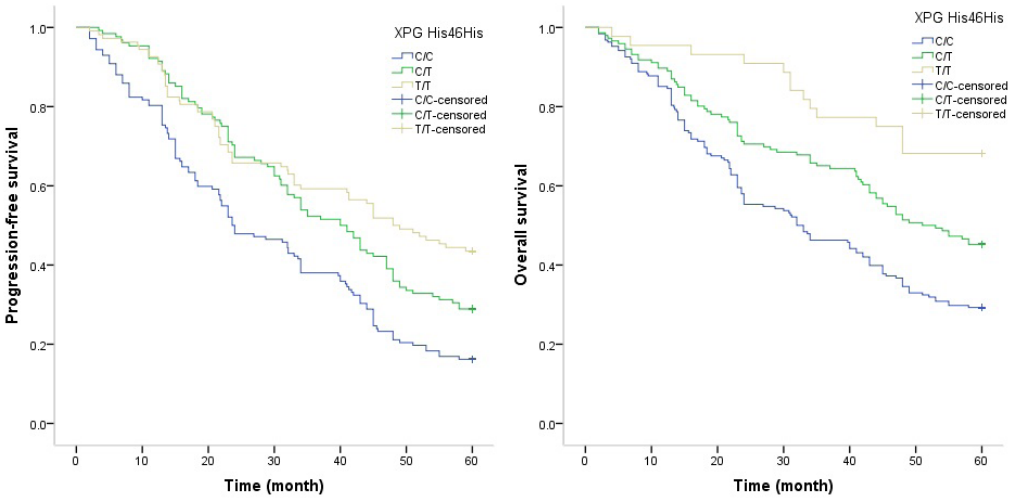

Figure 2. Kaplan-Meier estimates of disease-free survival and overall survival with the *XPG* His46His polymorphism.

DISCUSSION

In this study, we examined whether polymorphisms in 6 SNPs predicted to affect the metabolism of cisplatin and DNA repair could be used as predictors of the clinical outcome of platinum-based chemotherapy in NSCLC patients. Our results indicated that NSCLC patients with the A/A genotype in *XRCC1* Arg399Gln had a higher probability to positively respond to platinum-based treatment than those with the G/G genotype, indicated by increased overall survival of patients with the A/A genotype compared with that of patients with the G/G genotype. The polymorphism in *XRCC1* Arg399Gln has been associated with higher levels of DNA adducts, suggesting that this SNP variant results in deficient DNA repair (Lunn et al., 1999; Duell et al., 2000) and an increased efficacy of platinum-based chemotherapy. XRCC1 is a scaffold protein involved in the repair of single-strand breaks following BER. The codon 399 in the *XRCC1* gene is located within a BRCT (BRCA1 C-terminus) domain, believed to be a protein-protein interface that interacts with poly (ADP-ribose) polymerase involved in BER (Monaco et al., 2007). Although some studies have shown that *XRCC1* Arg399Gln is significantly associated with the prognosis of NSCLC, results from other studies have been inconsistent (Gurubhagavatula et al., 2004; Giachino et al., 2007; Sun et al., 2009). A study conducted in Taiwan reported that the *XRCC1* 399A/A genotype was associated with longer overall survival of its carriers (Liao et al., 2012). However, studies conducted in Italy have shown that *XRCC1* 399G/G is associated with a better survival of borderline significance among cisplatin-treated patients (Gurubhagavatula et al., 2004; Kalikaki et al., 2009). Studies conducted with individuals from an eastern Chinese population did not observe a significant association between *XRCC1* Arg399Gln and NSCLC treatment outcome (Sun et al., 2009; Yao et al., 2009). These inconsistent observations among the different studies may be explained by differences in genetic origin, population background, source of controls, sample size, or by other unknown factors in the subjects examined. Alternatively, gene-environment interactions may operate in the pathogenesis of NSCLC, and thus differences in environmental risk factors may affect NSCLC outcomes.

We also found a statistically significant association between the polymorphism in *XPG* His46His and clinical responses in NSCLC patients, with *XPG* 46G/G exhibiting an association with significantly decreased risk of NSCLC and a higher survival of cancer patients. Several studies have assessed the association between *XPG* His46His and cancer, including endometrial cancer, head and neck cancer, and gastric cancer (Cheng et al., 2002; Carles et al., 2006; Hussain et al., 2009; Doherty et al., 2011). A study conducted in the US with 783 endometrial cancer cases and 795 controls indicated that *XPG* 46G/G was associated with a decreased risk of death from cancer (Cheng et al., 2002). In addition, a study in China indicated that *XPG* 46G/G was associated with reduced gastric cancer risk (Hussain et al., 2009), whereas another indicated that *XPG* 46G/G was associated with shorter time to progression and survival (Carles et al., 2006). However, only one study has investigated the association between *XPG* 46G/G and prognosis of NSCLC, indicating that *XPG* 46G/G significantly affected the response to platinum-based chemotherapy (Sun et al., 2009), which is in agreement with the results of this study.

We note several limitations of this study. Although we adjusted for some potential risk factors in the prognosis of NSCLC, such as tumor histology, stage of diseases and smoking status, we did not collect other clinical factors that could also influence NSCLC prognosis. Moreover, because of the relatively small patient population, the association of *XRCC1* Arg399Gln and *XPG* His46His with NSCLC prognosis should be interpreted cautiously and should be validated in further studies. Nonetheless, because our study indicated that *XRCC1* Arg399Gln and *XPG* His46His might significantly affect the responses to chemotherapy, it is suggested that these two polymorphisms should be included in routine screening for NSCLC patients who are more likely to benefit from platinum-based chemotherapy. Larger studies are needed to confirm the roles of *XRCC1* Arg399Gln and *XPG* His46His in NSCLC.

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