

RESEARCH COMMUNICATION

Lack of Influence of XRCC1 and XPD Gene Polymorphisms on Outcome of Platinum-based Chemotherapy for Advanced Non Small Cell Lung Cancers

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Abstract

Purpose: Genetic polymorphisms of DNA repair genes are associated with differential enzyme activity and may help explain interindividual differences in response rates after platinum-based chemotherapy for non small cell lung cancers (NSCLCs). This study was conducted to assess relationships between X-ray repair cross complementing group1 (XRCC1) and xeroderma pigmentosum group D (XPD) genetic polymorphisms and outcome in NSCLC patients. **Methods:** From March 1, 2005 to December 31, 2008, the polymerase chain reaction-restriction fragment length polymorphism method was applied to evaluate genetic polymorphisms of the XRCC1 codon399 (Arg/Gln) and XPD codon751 (Lys/Gln) DNA repair genes in 108 patients with stage IIIB and IV NSCLCs treated with platinum-based chemotherapy in the Department of Chemotherapy of Jiangsu Cancer Hospital and Research Institute. **Results:** Among the assessed NSCLC patients, the overall response rate of chemotherapy was 21.6%. No association was found with either of the genetic polymorphisms, although the XRCC1 399Arg/Arg genotype was associated with a non-significant higher median survival time (29 months versus 21 months for the Arg/Gln genotype and 15 months for the Gln/Gln genotype, $P=0.09$). **Conclusion:** Our results suggested no influence of the XRCC1 codon399 (Arg/Gln) and XPD codon751 (Lys/Gln) genetic polymorphisms on treatment response and survival in advanced NSCLC patients with platinum-based chemotherapy.

Key Words: Non small cell lung cancer - platinum chemotherapy - DNA repair enzymes - genetic polymorphisms

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Introduction

Lung cancer is a leading cause of cancer-related death around the world. In China, the incidence of lung cancer is higher than any other cancers in men and is the second highest, after breast cancer, in women (Yang et al., 2005). The mortality rate of lung cancer is estimated to be 41.8 every one hundred thousand in men and 19.3 in women (Yang et al., 2004). Of all lung cancers, the non small cell lung cancers (NSCLCs) account for the majority, and close to 70% of the affected patients present with locally advanced or metastatic disease at the time of diagnosis (Molina et al., 2008). In terms of treatment for NSCLC, chemotherapy with a platinum-based doublet, continues to play a pivotal role, especially for those with stage II to IV disease (Bunn and Kelly, 1998; Sørensen et al., 2001; Pujol et al., 2006). However, the response rate of a platinum-based regimen is reported to be around 19% in advanced NSCLC patients with a median survival of only 7.9 months (Bosken et al., 2002; Schiller et al., 2002). How to improve this treatment result has long been a

research topic. Based on recent clinical studies, polymorphisms in DNA repair genes could be associated with chemotherapy sensitivity (Gurubhagavatula et al., 2004; Isla et al., 2004; Ryu et al., 2004; Rosell et al., 2005; Booton et al., 2006; de las Peñas et al., 2006; Giachino et al., 2007), suboptimal DNA repair possibly leading to decreased removal of platinum-DNA adducts and an increased clinical response to platinum therapy (Shellard et al., 1993; Bosken et al., 2002). One hypothesis is to deliver chemotherapy individually according to personal DNA repair ability.

However, repair of DNA damage is a complex process, involving an array of DNA repair pathways, which encompass both base excision repair (BER) and nucleotide excision repair (NER). It has been suggested that the X-ray repair cross complementing group1 (XRCC1) gene plays a direct role in BER by physically interacting with ligase III and poly (ADP-ribose) polymerase, which repair single-strand breaks, which is important in maintaining the stability of genome (Sancar et al., 2004). The xeroderma pigmentosum group D (XPD) gene encodes

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for a DNA helicase, which is a member of the multistep NER pathway, responsible for the majority of platinum-DNA adduct repair and featuring removal of a DNA segment with its associated bulky adduct, followed by the restoration of that DNA segment (Sung et al., 1993; Hoeijmakers et al., 1996; Reed, 1998; de Boer and Hoeijmakers, 2000; Lunn et al., 2000; Bosken et al., 2002).

Both the XRCC1 and XPD contain polymorphisms that may confer differential activity (Lunn et al., 2000; Butkiewicz et al., 2001). Thus, XRCC1 and XPD polymorphisms may contribute to interindividual DNA damage repair variability in the general population. Shen et al (1998) identified three coding polymorphisms in the XRCC1 gene at codons 194 (Arg/Trp), 280 (Arg/His) and 399 (Arg/Gln), resulting in nonconservative amino acid changes, which suggests potential functional relevance. The XRCC1 399Gln allele is associated with increased levels of DNA damage that may be due to reduced DNA repair function (Lunn et al., 1999). Several polymorphisms in the XPD gene have also been identified, Lunn et al (2000) compared the XPD codon312 (Asp/Asn) and codon751 (Lys/Gln) with DNA repair proficiency, and found possessing a Lys/Lys751 genotype increased the risk of suboptimal DNA repair. Several studies on genetic polymorphisms of XRCC1 codon399 (Arg/Gln) and XPD codon751 (Lys/Gln) in association with platinum-based treatment responses in NSCLC patients have already been reported in China (Wang et al., 2004; Yuan et al., 2005; 2006; Sun et al., 2009), but the results are still controversial and further studies are needed to address this questions.

The aim of the present work was therefore to prospectively assess the relationships of two single nucleotide polymorphisms (SNPs), the XRCC1 codon399 (Arg/Gln) and the XPD codon751 (Lys/Gln), with response and survival in a consecutive series of advanced NSCLC patients treated with platinum-based regimens.

Materials and Methods

Patient selection

All patients who were eligible to this study had histologically confirmed NSCLC, and were hospitalized at the Department of Chemotherapy of Jiangsu Cancer Hospital and Research Institute from 2005. The facility is located in Nanjing, China, and is a central Cancer Hospital in Jiangsu Province with 858 hospital beds. It serves about 80 million people of Jiangsu Province and neighboring regions. General information on this area can be found on the website:

<http://english.peopledaily.com.cn/data/province/jiangsu.html>.

Other eligibility criteria included: 1. Treated with platinum agents (cisplatin or carboplatin), either first or second line; 2. With measurable disease; 3. Eastern Cooperative Oncology Group (ECOG) performance status of 1 or 2; 4. Adequate organ function, defined as absolute neutrophil count > 1500/μL, platelet count >100,000/μL, and levels of creatinine, liver enzymes and alanine aminotransferase (ALT) less than two times the upper limits of normal (ULN). Patients were ineligible if they

had inadequate organ function, were pregnant or breast-feeding.

DNA extraction and genotyping

All patients enrolled into this study signed an informed consent before chemotherapy. Genomic DNA was extracted from peripheral blood lymphocytes. The genotypes of XRCC1 at codon399, and XPD at codon751 were determined by PCR-based restriction fragment length polymorphism (RFLP) methods as described previously (Xing et al., 2002). The primers were: 5'-CACCTAACTGGCATCTTCACTT-3' and 5'-ACAGGATAAGGAGCAGGGTT-' for the XRCC1 codon399 polymorphism; and 5'-CTTCATAAGACCTTCTAGCACCCAC-3' and 5'-TACGGACATCTCCAAATTCATTC-3' for the XPD codon751 polymorphism. PCR was performed in a 20 μl reaction mixture containing approximately 50 ng DNA, 12.5 pmol/μl each primer, 0.1 mM each dNTP, 2.0 mM MgCl₂, 1.0 U Taq DNA polymerase with 1 x reaction buffer (50 mM KCl, 10 mM Tris Hcl and 0.1% Triton X-100). Amplification of XRCC1 codon399 (Arg/Gln) and XPD codon751 (Lys/Gln) was carried out under the following conditions: an initial melting step of 5 min at 95 °C, followed by 35 cycles of 30 s at 95°C, 30 s at 52 °C and 45 s at 72 °C, and a final elongation of 10 min at 72 °C.

Response and survival assessment

Response was evaluated according to Response Evaluation Criteria in Solid Tumors, the revised version of the International Union Against Cancer/WHO criteria (WHO, 1979). Our primary end point was overall survival from the time of histologic or cytopathologic diagnosis to May 2009, and the second end point was the relationship between genetic polymorphisms and the treatment response. Dates of death were obtained and cross-checked using at least one of the following four methods: follow up by telephone; inpatient and outpatient medical records; documents of Ministry of Public Security; and confirmation with the patient's family. Dates of death were obtained most often through follow up by telephone.

Statistical methods

According to previous report, among oriental patients with advanced NSCLCs treated with platinum-based chemotherapy, the response rate is around 19% (Schiller et al., 2002). In terms of individual therapy, the response rate could be more than 60% (Mok et al., 2009). In our area, we suppose treatment based on genetic testing could be considered of clinical significance if the response rate exceeds 50%; Analyzed by STATA software under the condition that alpha=0.05 and statistical power=0.8, we should recruit at least 90 patients.

Demographic and clinical information was compared across genotypes, using Pearson χ^2 tests (for categorical variables) and one-way analysis of variance (for continuous variables), where appropriate. Associations between overall survival and the genetic polymorphisms (or the total number of variant alleles from both polymorphisms) were estimated using the method of

Table 1. Patient Characteristics, Treatment and Genotypes

Characteristic	No.	%
Age, years Median + Range	61	39-79
Sex		
Male	71	65.7
Female	37	34.3
Histology of cancer		
Adenocarcinoma	77	71.3
Squamous-cell	28	25.9
Large-cell	3	2.8
Stage		
IIIB	37	34.3
IV	71	65.7
Chemotherapy regimens		
Platinum + Gemcitabine	71	65.7
Platinum + Docetaxel	15	13.9
Platinum + Paclitaxel	17	15.7
Platinum + Vinorelbine	5	4.6
XRCC1 codon399 (Arg/Gln)		
Gln/Gln	60	55.6
Arg/Gln	43	39.8
Arg/Arg	5	4.6
XPD codon751 (Lys/Gln)		
Lys/Lys	86	81.1
Lys/Gln	20	18.9
Gln/Gln	0	0.0

Kaplan and Meier and assessed using the log-rank test. Logistic regression models were used to verify the relationship between chemosensitivity and genetic polymorphisms, adjusted for gender, age, stage, histology, performance status, and chemotherapy regimen. Factors influencing cancer death were estimated using a Cox proportional hazard model. All statistical analyses were performed using STATA software, version 7.0 (Stata Corporation, 4905 Lakeway Drive College Station, Texas 77845 USA).

Results

Patients and treatment

By the end of 2008, 108 patients met the study eligibility and were internalized. Treatment results of six patients and genotypes of the XPD at codon751 (Lys/Gln) of two patients were not available. Patient characteristics are displayed in Table 1, the majority having an Eastern Cooperative Oncology Group performance status of 1 and stage IV disease. Of the 102 patients assessable for chemotherapy response, 22 (21.6%) patients had a partial response, 50 (49.0%) had stable disease, and 30 (29.4%) had progressive disease. The median survival time (MST) was 18.5 months, in a range from 15 months in the stage IV patients to 21 months in the IIIB group.

Genetic polymorphisms and treatment response

XRCC1 codon399 (Arg/Gln) and treatment response. Table 2 shows the association of genotypes with treatment response in patients receiving platinum-based chemotherapy. The polymorphic genotypes of the XRCC1 codon 399 (Arg/Gln) were not significantly different between patients who responded and did not response to the platinum-based treatment. Among responders, 59.1% of patients carried at least one Arg allele (Arg/Arg or Arg/

Table 2. XRCC1 codon399 (Arg/Gln) and XPD codon751 (Lys/Gln) Polymorphisms and Chemotherapy Response in Advanced NSCLCs Analyzed by Logistic Regression

Genotype	CR+PR	SD+PD	OR*	95% CI	P-value
XRCC1	22	80	1.34	0.58-3.11	0.50
XPD	22	78	0.33	0.07-1.63	0.17

*Adjusted by gender, age, disease stage, histological type, performance status, and chemotherapy regimen; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; OR, odds ratio; CI, confidence interval

Table 3. XRCC1 codon399 (Arg/Gln) and XPD codon751 (Lys/Gln) Polymorphisms and Chemotherapy Response in Advanced NSCLCs Analyzed by the Cox Proportional Hazard Model

Genotype	HR* for death	95% CI	P-value
XRCC1	0.83	0.49-1.41	0.50
XPD	0.55	0.29-1.07	0.08

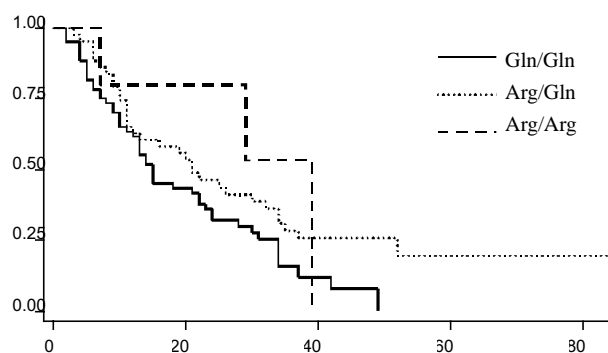
*Adjusted by gender, age, disease stage, histological type, performance status, and chemotherapy regimen; HR, hazard ratio; CI confidence interval

Gln), and 40.9% carried the Gln/Gln genotype. The corresponding figures for the non-responders were 40% and 60% respectively. After combining the Arg/Arg and Arg/Gln genotypes, the difference was still not statistically significant ($P=0.50$), the odds ratio (OR) for response was 1.34 and the 95% confidence interval (CI) was 0.58 to 3.11, after adjusting for gender, age, stage, histology, performance status, and chemotherapy regimen. No significance was found with the Cox proportional hazard model (see Table 3).

XPD codon751 (Lys/Gln) genetic polymorphisms and treatment response. Among responders, 90.0% of patients carried the Lys/Lys genotype and only 9.1% carried the Lys/Gln genotype. The corresponding figures for the non-responders were 78.2% and 21.8%. No association was found between the genotypes and the objective response (OR= 0.33; 95% CI, 0.07-1.63; $P=0.17$).

Genetic polymorphisms and overall survival

XRCC1 codon399 (Arg/Gln) and overall survival. Univariate analysis suggested no association of the Gln/Gln genotype of the XRCC1 with overall survival (log-rank test, $P=0.09$; Figure 1): the MSTs of individuals with

**Figure 1. Kaplan-Meier Estimates of the Survival Time (Months) for NSCLCs According to XRCC1399**

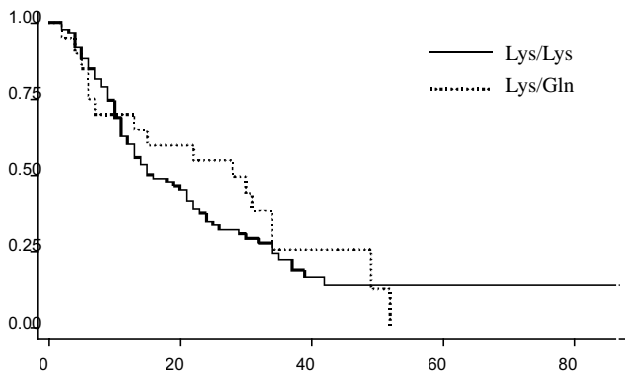


Figure 2. Kaplan-Meier Estimates of the Survival Time (Months) for NSCLCs According to XPD751

the Gln/Gln, Arg/Gln and Arg/Arg genotypes were 15, 21 (95% CI, 11.5-30.9) and 29 months (95% CI, 7.0-39.0 months), respectively. In the Cox proportional hazard model, after adjusting by gender, age, stage, histology, performance status and chemotherapy regimen, the hazard ratio (HR) for the genotypes of XRCC1 codon399 (Arg/Gln) was 0.83 (95% CI, 0.49-1.41; $P=0.50$).

XPD codon751 (Lys/Gln) and Overall Survival. In this study, the XPD codon751 (Lys/Gln) genotypes were not associated with decreased overall survival: patients with the Lys/Gln genotype had a MST of 26.5 months (95% CI, 7.7-33.8 months), those with the Lys/Lys genotype had a MST of 15.5 months (95% CI, 12.4-21.0 months; log-rank test, $P=0.50$; Figure 2). In the Cox multivariable model, after adjusting for gender, age, stage, histology, performance status, treatment regimen, the HR for Lys/Gln was 0.55 (95% CI, 0.29-1.07; $P=0.08$; Table 3).

Discussion

With advanced NSCLCs, cytotoxic chemotherapy continues to be the mainstay for initial treatment, but individualizing chemotherapy could deliver the most active agent to each patient (Rosell et al., 2005), and some promising pharmacogenomic predictors have been identified for efficacy and survival in advanced cases treated with platinum-based chemotherapy. However, from the present results, functional polymorphisms in the XRCC1 and XPD gene may not play important roles, despite the earlier publications pointing to links with DNA damage in lung cancer (Shen et al., 1998; Duell et al., 2000; Matullo et al., 2001; Spitz et al., 2001; Hu et al., 2004).

One similar result also showing no significant association between the XRCC1 codon399 (Arg/Gln) genotype and survival was reported (Sun et al., 2009), but in another study, the response rate to chemotherapy was significantly higher in patients with the 399Arg/Arg genotype (Wang et al., 2004). In the same way, increasing number of Gln/Gln genotype was linked with decreased overall survival in the study of Gurubhagavatula et al (2004), whereas Xing et al (2002) reported that the XRCC1 399Gln/Gln genotype was associated with a better survival following platinum-based chemotherapy.

XRCC1 has long been recognized as a key component of the BER pathway, acting as a "scaffold" for the

coordination of other BER proteins at the sites of base damage during repair (Sancar et al., 2004). In the repair of other types of cisplatin-induced damage, including double-strand breaks (DSBs), through a nonhomologous end-joining pathway, which is alternative to the predominant DNA-dependent protein kinase and Chinese hamster cells 4 (XRCC4)-DNA ligase IV complex pathway, XRCC1 may also be involved (Weaver et al., 2005). More than 60 SNPs in the XRCC1 gene have been validated and the most extensively studied are located at codons 194, 280, and 399, the latter is located in the critical carboxylic acid terminal side of the polyadenosine diphosphate-ribose polymerase-interacting domain, in an epidemiologic study, the XRCC1 codon 399 (Arg/Gln) was the most common and showed no major variations by ethnicity (Hung et al., 2005).

The XPD gene is absolutely necessary for NER, which is the major pathway for removal of bulky DNA lesions, particularly those induced by cigarette smoking (Chen et al., 2003). The XPD protein is a component of the core transcription factor IIIH, which is involved in NER of DNA by opening DNA around the damage. The helicase activity of XPD allows the opening of the double helix so that the damaged strand can be cut and the damaged piece of DNA removed. Polymorphisms in several exons of the XPD gene have been identified, two of them, codon312 (Asp/Asn) and codon751 (Lys/Gln), are common and result in an amino acid change. However, it may be only the joint effect of multiple polymorphisms within the gene that provides information about an association with lung cancer (Benhamou and Sarasin, 2005). The lack of any association found in the present study is in agreement with earlier findings for Chinese (Yuan et al., 2005; 2006) and other populations (de las Peñas et al., 2006; Giachino et al., 2007).

DNA repair can modulate the efficacy of cytotoxic agents, but this repair has been termed a double-edged sword because decreased DNA repair may increase the risk of developing cancer, although it might simultaneously improve survival in patients already diagnosed with cancer, when treated with platinum agents (Wei, et al., 2000; Rosell et al., 2002). Interpretation of the results is complicated by controversies regarding which genotypes confer decreased DNA repair activity; therefore, definitive conclusions are premature. Two reasons may explain our results. First, the process of drug metabolism could involve several steps that could be variable in individual patient. Second, it was uncertain that gene polymorphisms will result in a functional change of the encoded protein. So, the functional or biologic relevance of these polymorphisms should be further elucidated, and our results need to be confirmed by other studies.

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