Association of Base Excision Repair Gene Polymorphisms with the Response to Chemotherapy in Advanced Non-Small Cell Lung Cancer

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Abstract

Background: Base excision repair (BER) plays an important role in the maintenance of genome integrity and anticancer drug resistance. This study aimed to explore the role of *BER* gene polymorphisms in response to chemotherapy for advanced non-small cell lung cancer (NSCLC) patients treated with platinum-based chemotherapy.

Methods: During the period from November 2009 to January 2016, a total of 152 patients diagnosed with NSCLC Stage IIIB and IV in the First Hospital of Jilin University were admitted into this study. The *XRCC1 G28152A, MUTYH G972C, HOGG1 C1245G,* and *PARP1 T2444C* polymorphisms of all the patients were detected by mass spectrometry. The logistic regression was used for statictical analysis. All tests were bilateral test, and a *P* < 0.05 was considered statistically significant.

Results: The logistic regression model showed that the response rate of chemotherapy of the *PARP1 T2444C* polymorphisms, CC genotype (odds ratio [*OR*]: 5.216, 95% confidence interval [*CI*]: 1.568–17.352, *P* = 0.007), TC genotype (*OR*: 2.692, 95% *CI*: 1.007–7.198, *P* = 0.048), as well as the genotype of TC together with CC (*OR*: 3.178, 95% *CI*: 1.229–8.219, *P* = 0.017) were significantly higher than those of TT wild type. There was no relationship between the *MUTYH G972C, XRCC1 G28152A,* and *HOGG1 C1245G* gene polymorphisms and chemosensitivity.

Conclusions: The PARP1 2444 mutation allele C might be associated with the decreased sensitivity to platinum-based chemotherapy in advanced NSCLC. These findings may be helpful in designing individualized cancer treatment.

Key words: Base Excision Repair; Chemotherapy; DNA Repair; Genetic; Non-Small Cell Lung Cancer; Platinum; Polymorphism

INTRODUCTION

Non-small cell lung cancer (NSCLC) is one of the major causes of cancer-related death. The standard chemotherapy regimens are platinum-based doublets for advanced NSCLC patients without driver gene alterations. However, there are significant differences in the efficacy of platinum-based chemotherapy in NSCLC patients. The response rates differ from 26% to 60%, which indicates that patients show significant differences in the sensitivity to chemotherapy drugs.[1] Considering individual differences, an effective and convenient method is urgently required to identify the sensitivity of individual patients to a platinum-based regimen.

Platinum leads to cell death by damaging DNA through the cross-link chains or the chain cross-linking of DNA.[2]

Resistance is a difficult problem in the current treatment, and several studies on the mechanism of drug resistance have been performed. It is widely considered to be mainly due to the following four aspects:[3] decreased accumulation of platinum drugs, increased drug inactivation, enhancement of tumor cells' tolerance to platinum-DNA adducts, and enhancement of the repair of DNA damage. Increasing the DNA repair capacity leads to an increase in the removal

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of platinum-caused DNA adducts and therefore a decrease in clinical response.[4] DNA repair pathways include base excision repair (BER), nucleotide excision repair (NER), mismatch repair (MMR), and double-strand break (DSB) repair. The NER pathway, MMR pathway, and DSB pathway repair the damaged DNA after the formation of cross-link chains, while the BER pathway repairs it before the formation of cross-link chains.[5] Many clinical studies on the relationship between the *NER* gene polymorphisms and the response of advanced NSCLC treated with platinum-based chemotherapy have been performed. The results range from irrelevant to relevant.[6-8] Many studies show that the *NER* gene polymorphisms can be used to assess the prognosis and direct individual treatment in patients with NSCLC to a degree, but the results are controversial. Thus, the *NER* gene polymorphism cannot be an independent predictor.[9] There are a few studies on whether BER can influence the sensitivity of platinum-based chemotherapy, although the sample size is small and the influencing factors are poorly controlled, which requires further verification. Because both recognizing and excising play key roles in BER, we choose the *XRCC1 G28152A* and *PARP1 T2444C* polymorphisms, which play a role in recognition, and the *MUTYH G972C* and *HOGG1 C1245G* polymorphisms, which are genes for excision, to study the relationship between gene polymorphisms and the sensitivity of platinum-based chemotherapy in patients with NSCLC.

METHODS

Ethical approval

The study was approved by the Ethics Committee of the First Hospital of Jilin University and conducted according to the *Declaration of Helsinki*. All studied participants signed the written informed consent form.

Patients

In this study, we retrospectively recruited 152 NSCLC patients with clinical Stage IIIB and IV who were treated at the Cancer Center of the First Hospital of Jilin University between November 2009 and January 2016. All participants were local residents of Han descent. Eligible patients were confirmed by histology as having primary advanced stage NSCLC and were subjected to 4–6 cycles of platinum-based first-line chemotherapy (dose with reference to the NCCN guidelines for chemotherapy). The patients were not treated with other adjuvant therapies such as radiation therapy or immunotherapy, and the results of blood routine, liver and kidney function, and electrocardiogram were normal before the chemotherapy.

Tumor response

Tumor response was evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST) for measurable disease in combination with assessments of nonmeasurable disease. Treatment response (RECIST) outcomes were dichotomized by responders (complete response [CR] + partial response [PR]) and nonresponders (stable disease [SD] + progression

of disease [PD]). The therapeutic effect was evaluated every 3 weeks for one cycle and after two cycles of chemotherapy. Their responses were evaluated according to RECIST based on data from computed tomography scans. The efficacy evaluation for patients with CR or PR was defined as the chemotherapy-sensitive group, and the efficacy evaluation for patients with SD and PD was defined as the chemotherapy-insensitive group.

Sample collection and genotyping

Peripheral blood was withdrawn from all patients before chemotherapy, and genomic DNA was extracted from the peripheral blood lymphocytes using a Wizard® Genomic DNA Purification Kit A1125 (Promega, Madison, WI, USA). The DNA samples were subjected to allele-specific matrix-assisted laser desorption/ionization-time-of-flight (MALDI-TOF) mass spectrometry and MassARRAY (Sequenom, San Diego, CA, USA) analyses for the *XRCC1 G28152A, MUTYH G972C, HOGG1 C1245G,* and *PARP1 T2444C* gene polymorphisms. Primers and multiplex reactions were designed using RealSNP.com. Concordance among the three genomic control DNA samples present in duplicate was 100%. Of the single-nucleotide polymorphisms (SNPs) with genotyping data, the call rate was more than 95%. The steps were as follows: (1) the whole genome DNA (10 ng/L) OncoCarta polymerase chain reaction (PCR) primers and PCR amplification reagents were configured into a reaction system with a final capacity of 5 μl per pore in the 384 orifice plate by 2:2:1 solvent. The reaction conditions were initial denaturation 94°C 2 min; 94°C 30 s, 56°C 30 s, 72°C 1 min, 46 cycles; 72° extension 5 min. (2) The shrimp alkaline phosphatase (SAP): the SAP mixed reagent was added to the 384 hole PCR plate by 2 μl per pore, and the SAP reaction was carried out in the PCR instrument to dephosphorylate the free deoxynucleotide residues in the amplified reaction mixture to prevent the next step reaction. The reaction conditions were 37°C 40 min, 85°C 5 min, one cycle. (3) Primer extension reaction: the Type-PLEX extension reaction mixture was added to the 384 hole PCR plate by 2 μl per pore and extended reaction in the PCR instrument, and the insertion, deletion, replacement, and other polymorphisms in DNA were detected. The reaction conditions were: initial denaturation was 94°C 30 s, 94°C 5 s (52°C 30 s, 80°C 3 s, five cycles), 40 cycles; 72°C extends 3 min. (4) Extended desalination and mass spectrometric analysis: 6 mg resin desalt was added to the 384 hole PCR plate containing the final reaction sample; the MALDI-TOF mass spectrometer (Sequenom, San Diego, CA, USA) was applied to the Spector CHIP II matrix chip through MassARRAY Nanodispenser to analyze the mutations.

Statistical analysis

Statistical analyses were performed using SPSS software (version 20.0; SPSS, Chicago, IL, USA). Multiple factor logistic regression analysis was conducted to estimate odds ratios (*OR*s) and their 95% confidence intervals (*CI*s) for associations between each gene polymorphisms and the efficacy of chemotherapy in patients with advanced NSCLC.

SPSS software was used to generate two-sided *P* values, and a *P* < 0.05 was considered statistically significant.

RESULTS

Patients' characteristics

A total of 152 patients were enrolled in this study. There were 101 males and 51 females. The median age was 52 years (range: 39–76 years). There were 39 cases of squamous cell carcinoma, 107 cases of adenocarcinoma, and six cases of large cell carcinoma. There were 79 cases with smoking history (continuous or cumulative smoking for 6 months or more), 39 cases in clinical Stage IIIB, and 113 cases in IV Stage. One hundred and twelve cases of gemcitabine were treated with platinum group, 11 cases were combined with platinum and vinorelbine, six cases of paclitaxel combined with platinum group, and 23 cases of pemetrexed combined with platinum therapy. Epidermal growth factor receptor gene mutation was positive in 20 cases, negative in 14 cases, and undetected in 118 cases. The total effective rate of chemotherapy was 36.2%. The characteristics of the patients are shown in Table 1.

Genotype and treatment response

The distributions of genotypes and the efficiencies of different genotypes are shown in Table 2. In the sequencing analysis of *HOGG1 1245* and *PARP1 2444*, four of the 152 patients failed in sequencing due to sample problems. The logistic regression model showed that the effective rate

of chemotherapy of the *PARP1 T2444C* CC genotype was significantly higher than that of the TT wild type (*OR*: 5.216, 95% *CI*: 1.568–17.352, *P* = 0.007). The effective rate of chemotherapy of the TC genotype was higher than that of the TT wild type (*OR*: 2.692, 95% *CI*: 1.007–7.198, *P* = 0.048). The effective rate of chemotherapy in patients with at least one mutant gene (TC + CC) was higher than that in the wild type (*OR*: 3.178, 95% *CI*: 1.229–8.219, *P* = 0.017). The response rate of chemotherapy for the patients with the *PARP1 T2444C* TC or CC genotype was significantly higher than that of the TT wild-type patients. The logistic regression model showed that there was no relationship between the *HOGG1 C1245G*, *XRCC1 G28152A*, and *MUTYH G972C* gene polymorphisms and the efficacy of chemotherapy.

DISCUSSION

NSCLC is one of the major causes of cancer-related death. The standards of therapeutic regimens for NSCLC are platinum-based doublets, especially for advanced NSCLC patients. However, there are significant differences in the efficacy of platinum-based chemotherapy in advanced NSCLC patients. The BER pathway plays an important role in platinum-induced DNA damage repair. Our data demonstrated that the *PARP1 2444* mutation allele C may be associated with decreased sensitivity to platinum-based chemotherapy in advanced NSCLC. There is no relationship between *XRCC1 G28152A*, *MUTYH G972C*, and *HOGG1 C1245G* gene polymorphisms and chemosensitivity.

PARP1 2444 site gene mutations decrease the resulting protein's ability to repair damaged DNA, so for the patients carrying the mutated genes, it may be possible to increase the patient sensitivity to platinum drugs.[10] This study showed that the response rate of chemotherapy for *PARP1 T2444C* mutation carriers was significantly higher than that of the wild type and that the response rate of the patients with the CC homozygous mutant genotype was significantly higher than that of the TT wild type. The results of our study are consistent with *PARP1 2444* gene mutations on the influence of the mechanism of the DNA damage repair ability. Therefore, we believe that the *PARP1 2444* polymorphisms may be used as a predictor of the efficacy of platinum in treating advanced NSCLC. Some published studies did not find a relationship between the *PARP1 T2444C* polymorphisms and the sensitivity to platinum-based chemotherapy in advanced NSCLC.[11,12] The differences may be limited by the sample size of those studies and the differences in genetic variation among different races. In addition, the current studies are nonrandomized controlled retrospective study, which may influence the accuracy of the result. We will expand the sample size in the future by doing further research to confirm our findings. Moreover, it is necessary to further improve the experimental design to make the result more credible.

This study shows that *XRCC1 G28152A* SNPs can change their DNA repair activity and thus affect the sensitivity of tumor cells to platinum drugs.[13] There is a great controversy

Table 1: Characteristics of the NSCLC patients

Characteristics	*n* (%)
Sex	
Male	101 (66.4)
Female	51 (33.6)
Age	
<60 years	90 (59.2)
≧60 years	62 (40.8)
Histology	
Squamous cell carcinoma	39 (25.7)
Adenocarcinoma	107 (70.4)
Large cell lung cancer	6 (3.9)
Smoking history	
Never smokers	73 (48.0)
Smokers	79 (52.0)
Clinical stage	
IIIB	39 (25.7)
IV	113 (74.3)
First line chemotherapy	
Gemcitabine + platinum	112 (73.7)
Navelbine + platinum	11 (7.2)
Paclitaxel + platinum	6 (4.0)
Pemetrexed + platinum	23 (15.1)
EGFR gene mutation	
Positive	20 (13.2)
Negative	14 (9.2)
Undetected	118 (77.6)

NSCLC: Non-small cell lung cancer.

Table 2: Associations between patient gene polymorphisms and the efficiency of chemotherapy, *n* (%)

Genotype	*n*	CR + PR	SD + PD	*OR (95% CI)*	*P*	*OR (95% CI)**	*P**
XRCC1							
GG	83	34 (41.0)	49 (59.0)	1.000		1.000	
GA	62	18 (29.0)	44 (71.0)	0.59 (0.292–1.189)	0.140	0.480 (0.220–1.048)	0.065
AA	7	3 (42.9)	4 (57.1)	1.081 (0.227–5.141)	0.922	3.145 (0.540–18.322)	0.202
AA + GA	69	21 (30.4)	48 (69.6)	0.631 (0.321–1.237)	0.180	0.548 (0.261–1.149)	0.111
MUTYH							
GG	65	24 (36.9)	41 (63.1)	1.000		1.000	
GC	69	27 (39.1)	42 (60.9)	1.098 (0.546–2.208)	0.793	1.238 (0.551–2.780)	0.605
CC	18	4 (22.2)	14 (77.8)	0.488 (0.144–1.653)	0.249	0.286 (0.069–1.183)	0.084
CC + GC	87	31 (35.6)	56 (64.4)	0.946 (0.485–1.844)	0.870	0.944 (0.438–2.035)	0.833
HOGG1							
CC	23	5 (21.7)	18 (78.3)	1.000		1.000	
CG	58	23 (39.7)	35 (60.3)	2.366 (0.770–7.264)	0.132	2.227 (0.643–7.716)	0.207
GG	67	25 (37.3)	42 (62.7)	2.143 (0.708–6.487)	0.177	2.287 (0.675–7.752)	0.185
GG + CG	125	48 (38.4)	77 (61.6)	2.244 (0.782–6.441)	0.133	2.259 (0.706–7.230)	0.170
PARP1							
TT	44	9 (20.5)	35 (79.5)	1.000		1.000	
TC	76	28 (36.8)	48 (63.2)	2.269 (0.952–5.405)	0.064	2.692 (1.007–7.198)	0.048
CC	28	15 (53.6)	13 (46.4)	4.487 (1.581–12.735)	0.005	5.216 (1.568–17.352)	0.007
CC + TC	104	43 (41.3)	61 (58.7)	2.741 (1.195–6.287)	0.017	3.178 (1.229–8.219)	0.017

*Adjusted by sex, age, pathological type, clinical staging, smoking history, and first-line chemotherapy. *OR*: Odds ratio; *CI*: Confidence interval; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progression of disease.

between the results about the influence of the sensitivity of chemotherapy of clinical research at home and abroad. We found no relationship between the *XRCC1 G28152A* SNPs and the sensitivity to platinum-based chemotherapy. Some studies showed that there was no relationship between them,[14,15] while other studies have found that the sensitivity of GG wild-type patients to chemotherapy was significantly higher than that of patients carrying at least 1 A allele,[16] and the response rate of GA or AA genotype carriers was significantly higher than that of patients with type GG.[17,18] The response rate of chemotherapy in our research was 36.2%, which was similar to that of other studies. However, in our study, the distribution of the *XRCC1 G28152A* genotype was not balanced. There were only seven patients with the AA genotype, and the sample size of the AA genotype was so small that the results of our study were not sufficient to explain the exact relationship between *XRCC1 G28152A* gene polymorphisms and the sensitivity to platinum-based chemotherapy. We must expand the sample size to continue to explore the relationship between *XRCC1 G28152A* gene polymorphisms and the efficacy of platinum-based chemotherapy for advanced NSCLC. In addition, the differences in research results may be related to different ethnic groups.

After DNA replication, DNA *MUTYH* scans the subchain rapidly and cuts off the 8-oxodG mismatch A of the mother chain, but the effect of the *MUTYH 972* site gene mutation on the function of *MUTYH* in the repair of damaged DNA is still inconclusive.[19] Our study did not find a correlation between the *MUTYH G972C* polymorphisms and the sensitivity of platinum-based chemotherapy to treat the patients with advanced NSCLC. Most studies have been performed to investigate the relationship between the

MUTYH (G>C rs3219489) polymorphism and the prognosis of advanced NSCLC patients treated with platinum-based chemotherapy. However, there are few studies on its influence on the sensitivity of the platinum-based treatment. Currently, published studies have shown that the *MUTYH* (G>C rs3219489) polymorphism is not associated with survival in patients with lung cancer.[20,21]

C/G transformation of the 1245th base of the 7th exon of the *HOGG1* gene on the 326th codon can encode serine (Ser) or cysteine (Cys), which can produce either Ser326 or Cys326 proteins. The latter amino acid residue reduces the ability of *HOGG1* to repair 8-hydroxyguanosine,[22] thus enhancing the sensitivity of platinum. In our study, we compared the efficiency of chemotherapy of different genotypes, and the results showed that the response rate of chemotherapy in patients with the *HOGG1 1245* GG genotype was higher than that in wild-type patients. Patients with at least one variant gene G had a higher rate of chemotherapy than that of CC wild-type patients, but there were no statistically significant differences. In a clinical study that examined 150 patients with platinum-treated advanced NSCLC for the relationship between *HOGG1 G1245C* gene polymorphisms and the sensitivity of the treatment,[23] the study defined the evaluated efficacy of CR, PR, and SD as beneficial chemotherapy and the efficacy of PD as ineffective. The results showed that the rate of beneficial chemotherapy in patients with the GG genotype was significantly higher than that in wild-type patients. Although there was no statistically significant difference in the sensitivity of this study, the *HOGG1 1245* site mutation gene G would be likely to be a sensitive predictor of platinum-based chemotherapy.

In summary, our data demonstrated that the *PARP1 2444* mutation allele C may be associated with decreased sensitivity to platinum-based chemotherapy in advanced NSCLC cancer, and few published studies have shown this finding. Our findings may be helpful toward designing individualized cancer treatment. The accuracy of the retrospective study has some limitations. There may be interactions between different gene polymorphisms; co-analysis of gene polymorphisms may be more helpful in guiding the individualized treatment. The DNA repair gene polymorphisms were influenced by the number of cases, chemotherapy regimens, genotype detection methods, and the distribution frequency of race genes. Therefore, whether genetic polymorphism of *PARP1 2444* can be used as a basis for individualized treatment is still need to be verified by large prospective clinical trials.

Conflicts of interest
There are no conflicts of interest.

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碱基切除修复基因多态性与晚期非小细胞肺癌化疗疗效的关系

摘要

目的：碱基切除修复通路(BER)在维持基因完整性和抗肿瘤耐药性中起着重要作用。本研究旨在探讨BER基因多态性与铂类治疗晚期非小细胞肺癌(NSCLC)疗效的关系。

方法：收集 2009 年 11 月~2016 年 1 月，在吉林大学第一医院收治并经病理学确诊的IIIB 或IV 期符合研究标准的 152 例非小细胞肺癌(NSCLC)患者。采用质谱法检测*XRCC1 G28152A*、*MUTYH G972C*、*HOGG1 C1245G*及*PARP1 T2444C*基因多态性，对测定结果通过 logistic 回归模型进行统计学分析。

结果：Logistic 回归模型示 PARP1 T2444C的CC基因型化疗有效率显著高于TT野生型 (*OR*:5.216， 95%*CI*: 1.568-17.352，*P* =0.007);TC基因型化疗有效率高于TT野生型 (*OR*: 2.692，95%*CI*: 1.007-7.198，*P* =0.048);携带TC基因型或CC基因型的患者的化疗有效率高于 TT 基因型患者(*OR*:3.178，95%*CI*: 1.229-8.219，*P* = 0.017)。*XRCC1 G28152A*、*MUTYH G972C*及*HOGG1 C1245G*基因多态性与化疗敏感性之间均未发现显著相关性。

结论：携带*PARP1 2444* 位点的等位基因C可能与铂类联合方案治疗晚期非小细胞肺癌的敏感性降低有关。我们的研究结果可能有助于指导肿瘤的个体化治疗。