·Basic Research·

# Correlation of the sensitivity to vinorelbine plus cisplatin (NP) chemotherapy with polymorphism in the DNA repair gene XRCC1 in non-small lung cancer

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**[Abstract] Background and Objective:** The gene polymorphism is used to predict sensitivity to chemotherapy, which is significant for individualized treatment of cancer. This study explored the correlations of codon 194 and codon 399 polymorphisms of DNA repair gene X-ray repair cross complementing (XRCC1) with the sensitivity of patients with non-small cell lung cancer (NSCLC) to vinorelbine and cisplatin (NP) chemotherapy. **Methods:** In 164 patients, XRCC1 polymorphisms at codon 194 and codon 399 were detected using a polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP). Patients administered NP were evaluated after two cycles of treatment, then the correlation of the sensitivity to chemotherapy with polymorphisms was analyzed. **Results:** Patients with the XRCC1 codon 194 C/T+T/T polymorphisms were 1.038 times more sensitive to the treatment than patients with the C/C genotype ($P$= 0.036, 95% CI = 1.044–3.976). There was no significant difference in the efficacy of chemotherapy for patients with the XRCC1 codon 399 G/A polymorphism. Using the SHEsis statistical software, the efficacy of chemotherapy for the T-A haplotype significantly increased compared with other haplotype groups ($P$= 0.031) while that of the C-A haplotype significantly decreased compared to others ($P$= 0.035). **Conclusions:** The sensitivity to NP in patients with NSCLC who carry XRCC1 codon 194 CT and TT genotypes increased significantly compared to those with the CC genotype. XRCC1 codon 194 and codon 399 polymorphisms may be useful in clinical applications to predict the sensitivity to NP in patients with NSCLC.

**Key words:** DNA repair gene, X-ray repair cross complementing 1 (XRCC1), polymorphism, lung neoplasm, non-small cell carcinoma, NP chemotherapy, chemotherapy sensitivity

Primary bronchogenic carcinoma, also known as lung cancer, is one of the most common malignant tumors, with the highest incidence and mortality among all malignant tumors. In non-small cell lung cancer (NSCLC), the most common type of lung cancer, patients are often diagnosed at later stages, and the treatment is primarily a chemotherapy-based integrated strategy. Vinorelbine plus cisplatin, commonly referred to as NP, is the first-line chemotherapy regimen that is used most often. As a cell-cycle-specific agent against mitosis, vinorelbine arrests cells in the mitosis metaphase during cell division by interfering with the assembly of microtubulin into microtubules and inducing the degeneration of microtubules. DNA is the target of cisplatin; as a non-cell-cycle-specific agent, cisplatin interferes with DNA replication by acting on inter- and intrastrand crosslinks and forming a cisplatin-DNA complex, or by binding to nucleoproteins or cytoplasmic proteins.

Efficacy of antitumor treatment is related to individual characteristics of the cancer.[1] Different patients with cancer may have different responses to the same treatment. Even with the same clinical diagnosis, staging and general status, and the same therapeutic dosage of the same agents, they may still present different efficacy and adverse reaction profiles. Studies suggest that the ability to repair damaged DNA varied vastly from individual to individual.[2]

The x-ray repair cross complementing 1 (XRCC1) gene is an important component in DNA base excision repair and single-strand break repair systems. By interacting with poly (ADP-ribose) polymerase, DNA ligase, and DNA polymerase β, XRCC1 repairs the damage induced by various physical and chemical factors, including cisplatin, and thus has an important role in maintaining genomic stability.[3] Studies have reported

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polymorphisms in codons 194 and 399 of XRCC1.[4,5] These polymorphisms were reported to be related to the sensitivity of patients with NSCLC to chemotherapy.[6-10] But most of these studies failed to take into account the influence of the different chemotherapy regimens the patients had undergone. If we rigorously define the type of chemotherapy, while excluding the influence on sensitivity to chemotherapy from numerous factors, such as sex, age, smoking history, pathological classification, and clinical staging, we can better uncover the correlation between gene polymorphism and sensitivity to chemotherapy in patients with NSCLC, and avoid the potential influence of differences in chemotherapy on the study results.

Based on well-controlled and balanced inclusion criteria for the patients, our study investigated the association of XRCC1 gene polymorphisms and sensitivity to NP in patients with NSCLC who used the same chemotherapy regimen (NP regimen).

## Materials and Methods

### Study subjects

Study subjects included 164 patients with advanced stage NSCLC treated in the Oncology Department of the First Affiliated Hospital of China Medical University and the Oncology Department of the Oncology Hospital of Liaoning Province between October 2006 and October 2007. Among them, 99 were men and 65 were women. They aged from 27 to 84 years, with a median age of 61 years. Complete records were available in 159 patients; the record of smoking history was inavailable in three patients; the records of pathologic classification and clinical stage were inavailable in one patient. All patients with evaluable and measurable lesions were pathologically or cellularly confirmed and all were treated with NP. Before beginning treatment, written informed consent was obtained from patients. An amount of 5 mL venous blood was taken from the patients after fasting and placed into anticoagulated tubes. Serum and sludged blood were separated and preserved below -20℃. General information about patients in our study, including sex, age, smoking history, pathologic classification, and clinical stage, is shown in Table 1.

**Table 1 The primary characteristics of 164 patients with non-small cell lung cancer (NSCLC)**

| Variable | Number | Percentage(%) |
|---|---|---|
| Gender | | |
| Male | 99 | 60.4 |
| Female | 65 | 39.6 |
| Age (years) | | |
| ≤61 | 86 | 52.4 |
| >61 | 78 | 47.6 |
| Smoking | | |
| Yes | 89 | 54.3 |
| No | 72 | 43.9 |
| Pathologic type | | |
| Squamous carcinoma | 70 | 42.7 |
| Adenocarcinoma | 93 | 56.7 |
| Clinical stage | | |
| Ⅲ | 100 | 60.9 |
| Ⅳ | 63 | 38.4 |

The date of some patients are incomplete.

### Detection of XRCC1 polymorphisms

Genotype analysis was performed on codons 194 and 399 of XRCC1 using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). An amount of 500 μL of plasma was obtained from a -20℃ freezer and was placed into a 2-mL centrifuge tube for DNA extraction. To the plasma was added 800 μL of TE buffer solution. The mixture was well blended and then underwent centrifugation at 10 000 r/min for 10 min at room temperature. The centrifugation process was repeated 5-6 times, until the plasma was not visible and the DNA was completely dissolved in the TE. Another 400 μL of TE was added, together with 25 μL of 10% sodium dodecyl sulfate (SDS) and 5 μL of 20 mg/mL pyruvate kinase (PK). The mixture was digested overnight at 37℃. After that, the supernatant fluid was removed, and phenol was added at equal volume. The mixture was oscillated for 15 min and centrifuged at 10 000 r/min for 10 min. Again, the supernata nt fluid was removed, and equal parts of phenol to chloroform (1:1) were added at equal volume. The mixture was then oscillated for 15 min and was centrifuged at 10 000 r/min for 10 min. With the supernatant fluid removed, chloroform was added to an equal amount, and the mixture underwent another cycle of oscillation (15 min) and centrifugation (10 min at 10 000 r/min). After the supernatant fluid was removed, anhydrous alcohol was added at twice the volume and the 3 mol/L solution of sodium acetate was added at 1/10 volume. The solution was stored at -20℃ for 1 h for precipitation, then underwent centrifugation at 10 000 r/min for 10 min. The supernatant fluid was removed, and 75% ethanol was added to the precipitation, which was then centrifuged at 10 000 r/min for 5 min. The supernatant fluid was removed and the precipitation was dried. A total of 100 μL of TE solution was added and the tube was placed into a -20℃ freezer and preserved for subsequent measurements.

In detecting the polymorphisms of codons 194 and 399 in XRCC1, the primers used in polymorphism detection of codon 194 (C/T) in XRCC1 were 5'-GCCCCGTCCCAGGTA-3' and 5'-AGCCCCAAGACCCTTTCACT-3' (the length of the amplified product was 490 bp). Primers in the polymorphism detection of codon 399 (G/A) of XRCC1 were 5'-TCTCCCTTGGCTCCAACCT-3' and 5'-AGTAGTCTGCTGGCTCTGG-3' (the length of the amplified product was 402 bp). The PCR reaction system (50 μL) contained 5 μL of 10× PCR buffer solution (with $MgCl_2$ 25 nmol/L), 4 μL of 2.5 mmol/L mixture of 4 dNTPs (50 μmol/L), l μL of varied primers (0.2 μmol/L), 0.5 μL of *Taq* DNA polymerase (2.5 U), 1 μL of template DNA (50-100 ng), with double-distilled water added to the volume of 50 μL. PCR was catalyzed at 95℃ for 3 min for predenaturation, and then 35 cycles of 30 s at 94℃, 45 s at 61℃, 45 s at 72℃, and finally 7 min at 72℃ for elongation. An amount of 12 μL of the PCR product was incubated overnight at 37℃ with restriction endonuclease *Pvu* Ⅱ (against codon 399; by MBI) or *Bcn* Ⅰ (against codon 399; by

MBI). All these cleavaged products underwent electrophoresis in 2.0% agarose gel (with 0.5 μg/mL EB). The electrophoresis results were observed and analyzed by the gel imaging system HVE50. Based on restriction sites, mutated codon 194 (C→T) of XRCC1 was recognized by *Pvu* Ⅱ and the amplified product cleavaged into 2 segments of 294 bp and 196 bp. Three segments of 490 bp, 294 bp, and 196 bp were produced in the heterozygous genotype, while only one segment of 490 bp was generated in the wild-type genotype. Mutated codon 399 (G→A) of XRCC1 lost the restriction site for *Bcn* Ⅰ, and thus only one segment of 402 bp could be produced. In the wild-type genotype, the codon was recognized by *Bcn* Ⅰ and the amplified product cleavaged into 2 segments of 269 bp and 133 bp. Three segments of 402 bp, 269 bp, and 133 bp were produced in the heterozygous genotype. The PCR products of codons 194 and 399 were further purified and sequenced.

### Chemotherapy regimen and efficacy evaluation in NSCLC

**Chemotherapy regimen (NP)** Vinorelbine (25 mg/m$^2$) in 100 mL of 0.9% normal saline was given via intravenous drip on day 1 and day 8, and cisplatin (40 mg) in 500 mL of 0.9% normal saline was given via intravenous drip on days 2–4 every 21 days. At the end of the second cycle, efficacy was evaluated for measurable lesions.

**Efficacy evaluation** Based on World Health Organization (WHO) criteria (1981), complete remission (CR) was defined as the complete disappearance of measurable lesions, partial remission (PR) was defined as shrinkage of measurable lesions by ⩾ 50%, no change (NC) was defined as shrinkage of less than 50% or enlargement of less than 25% in measurable lesions, and progressive disease (PD) was defined as enlargement by more than 25% in one or more lesions or the development of new lesions. CR and PR indicated effectiveness (and were included in the calculation of response rate), while NC and PD suggested ineffectiveness.

### Statistical methods

Statistical analysis was processed with SPSS version 11.5. The frequency of alleles was calculated. Distribution of genotype in different groups was compared using a $\chi^2$ test, with odds ratio (OR) and its 95% confidence interval (CI) indicating the relative hazard ratio. The frequency of haplotype was calculated with SHEsis software.[11] $P$<0.05 indicated statistical significance.

## Results

### Distribution of the XRCC1 genotype and total response rate to chemotherapy

The PCR-amplified products of codons 194 and 399 of XRCC1 underwent restricted enzyme digestion and electrophoresis, which revealed C/C, C/T, and T/T genotypes, and G/G, A/G, and A/A genotypes, respectively (Fig. 1). The polymorphisms of codons 194 (C/T) and 399 (G/A) were further confirmed by sequencing the PCR products (Fig. 2). In the 164 patients with NSCLC, the occurrence of C/C, C/T, and T/T genotypes in codon 194 of XRCC1 were 46.34% (76 patients), 42.07% (69 patients), and 11.59% (19 patients), respectively. The presence of G/G, A/G, and A/A genotypes in codon 399 were 44.51% (73 patients), 44.51% (73 patients), and 10.98% (11 patients), respectively. With NP chemotherapy, CR was reported in 3 patients, PR in 54 patients, NC in 87 patients, and PD in 20 patients, with a total response rate of 34.76%.

### Correlation between polymorphisms of XRCC1 and sensitivity to chemotherapy

Single-variate analysis was performed on sex, age, smoking status, pathologic classification, and clinical stage to reveal the influence on the sensitivity to chemotherapy in patients with NSCLC (Table 2). The results suggested an insignificant influence on sensitivity to chemotherapy from these factors (all $P$>0.05).

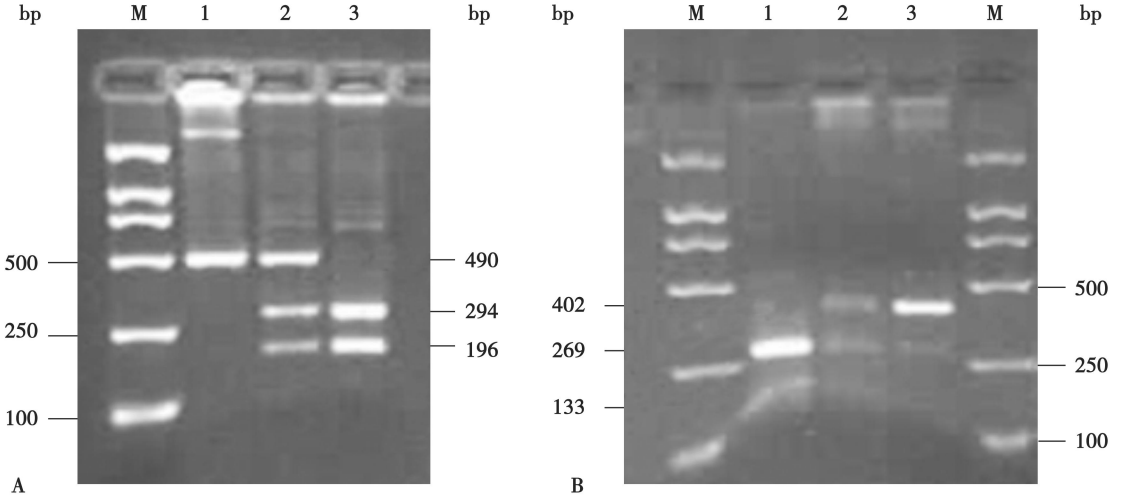


Figure 1 Identification of X-ray repair cross complementing (XRCC1) genotypes using polymerase chain reaction (PCR) restriction fragment length polymorphism

M: marker; DNA marker is DL2000. A, the three fragments of XRCC1 codon194 incised by *Pvu* Ⅱ restriction enzyme are 490,294, and 196 bp, respectively; 1, C/C homozygote; 2, C/T heterozygote; 3, T/T homozygote. B, the three fragments of XRCC1 codon399 incised by *Bcn* Ⅰ restriction enzyme are 402, 269, and 133 bp, respectively; 1, G/G homozygote; 2, G/A heterozygote; 3, A/A homozygote.

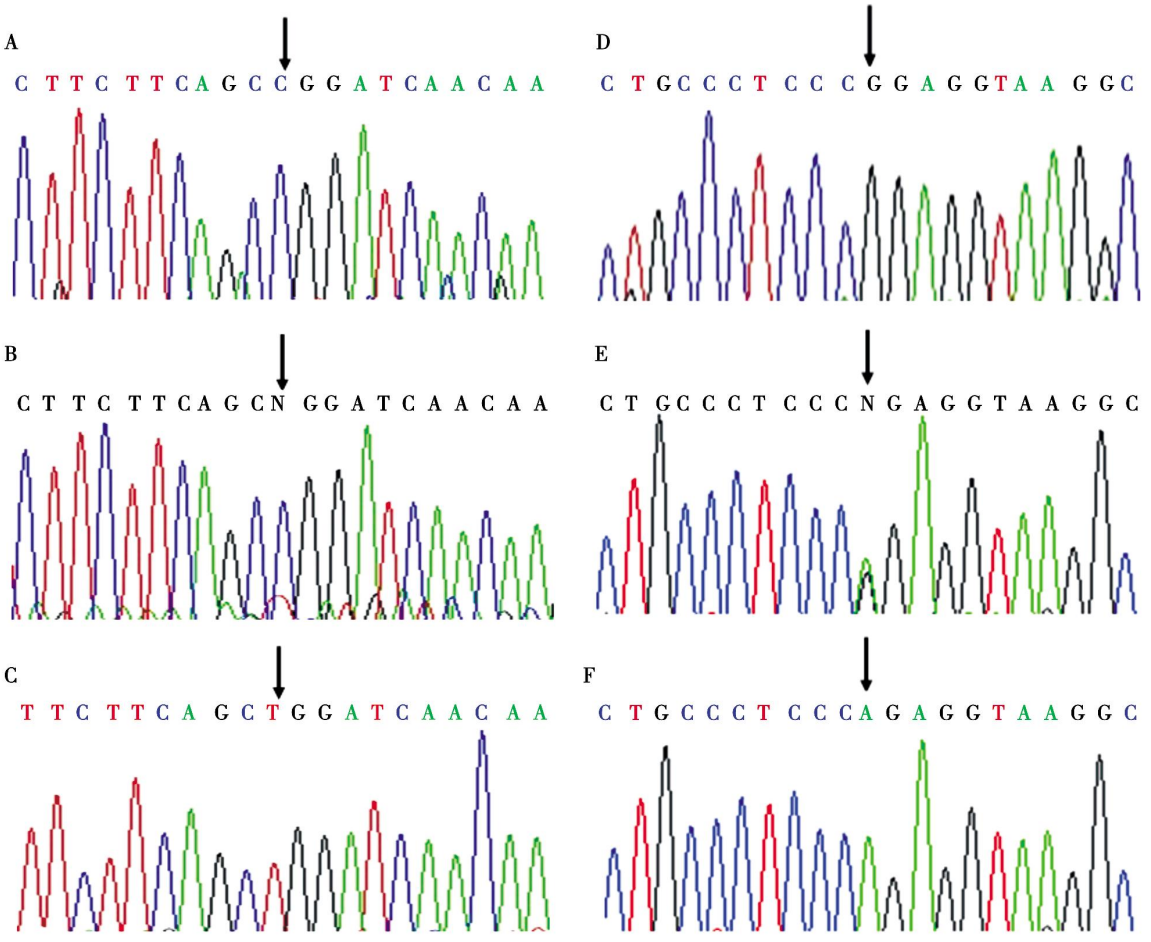


Figure 2 The sequencing results of the PCR products of XRCC1 gene codon 194 and codon 399 polymorphism

The arrows refer to the base of XRCC1 gene polymorphism. A, 194 C/C genotype; B, 194 C/T genotype; C, 194 T/T genotype; D, 399 G/G genotype; E, 399 G/A genotype; F, 399A/A genotype.

**Table 2 Association between clinicopathologic factors and sensitivity to chemotherapy in patients with NSCLC**

| Variable | The effect of chemotherapy | | $\chi^2$ | *P* | OR | 95% CI |
|---|---|---|---|---|---|---|
| | Ineffective [number (%)] | Effective [number (%)] | | | | |
| Gender | | | | | | |
| Male | 68(68.7) | 31(31.3) | | | 1 | |
| Female | 39(60.0) | 26(40.0) | 1.306 | 0.253 | 1.462 | 0.761-2.780 |
| Age (years) | | | | | | |
| ≤61 | 56(65.1) | 30(34.9) | | | 1 | |
| >61 | 51(65.4) | 27(34.6) | 0.001 | 0.971 | 0.988 | 0.519-1.881 |
| Smoking | | | | | | |
| No | 55(61.8) | 34(31.2) | | | 1 | |
| Yes | 51(70.8) | 21(29.2) | 1.445 | 0.449 | 0.666 | 0.343-1.294 |
| Pathologic type | | | | | | |
| Squamous carcinoma | 46(65.7) | 24(34.3) | | | 1 | |
| Adenocarcinoma | 60(64.5) | 33(35.5) | 0.025 | 0.874 | 1.054 | 0.550-2.022 |
| Clinical stage | | | | | | |
| Ⅲ | 67(67.0) | 33(33.0) | | | 1 | |
| Ⅳ | 39(61.9) | 24(38.1) | 0.441 | 0.507 | 1.249 | 0.647-2.411 |

The data of some patients are imcomplete. OR, adds ratio; CI, confidence interval.

Further analysis on the relationship between codon 194 and 399 of XRCC1 and sensitivity to chemotherapy in patients with NSCLC revealed a significant difference in response rates to chemotherapy between patients with the C/T genotype in codon 194 and those with the C/C genotype ($P$=0.036) (Table 3). Patients with the C/T genotype were 1.098 times more sensitive to chemotherapy than those with the C/C genotype (OR = 2.098; 95% CI = 1.043–4.220). Since patients carrying the T/T genotype in codon 194 were rare (18/164, 10.97%), patients with the C/T genotype and those with the T/T genotype were included as a C/T+T/T genotype group in the analysis. The analysis revealed a significant difference in the response rate to chemotherapy between patients with the C/T+T/T genotype and those with the C/C genotype ($P$=0.036), and patients with a T allele were 1.038 times more sensitive to chemotherapy than those with the C/C genotype (OR = 2.038; 95% CI = 1.044–3.976). The response rates in patients with G/G, A/G, and A/A genotypes in codon 399 of XRCC1 were 37.1%, 34.6%, and 14.3%, respectively. No significant differences were seen between them ($P$>0.05).

## Correlation between the joint influence of polymorphisms in codons 194 and 399 of XRCC1 and sensitivity to chemotherapy

Analysis was performed to reveal the correlation between the joint influence of polymorphisms in codons 194 and 399 of XRCC1 and the efficacy of chemotherapy. Among patients with both the C/T genotype in codon 194 and the G/C genotype in codon 399, 14 were included in the effective group and 14 in the ineffective group, with a response rate of 50%. When compared to the response rates in patients with other genotypes (43/136, 31.4%), the difference was not significant ($P$=0.063; Table 4).

## Linkage disequilibrium and haplotype analyses on the polymorphisms in codons 194 and 399 of XRCC1

SHEsis was used to conduct haplotype analysis on 2 single nucleotide polymorphism (SNP) sites of codons 194 and 399 in XRCC1. In patients on our study, 4 haplotypes could be seen on the 2 SNP sites. As compared to patients with other haplotypes, patients with the T-A haplotype had significantly increased response rates to chemotherapy ($P$=0.031), while those with the C-A haplotype had decreased response rates ($P$=0.035). Compared to individuals with other haplotypes, those with the T-A haplotype had a 2.486-fold higher response to chemotherapy (95% CI = 1.061–5.829), while those with the C-A haplotype had a 55.1% lower response to chemotherapy (95% CI = 31.6% –96.2%) (Table 5).

**Table 3 Correlation of X-ray repair cross complementing (XRCC1) codon 194 and codon 399 polymorphisms with sensitivity to chemotherapy in NSCLC patients**

| Variable | The effect of chemotherapy | | $\chi^2$ | $P$ | OR | 95% CI |
|---|---|---|---|---|---|---|
| | Ineffective [number(%)] | Effective [number (%)] | | | | |
| 194C/T polymorphism | | | | | | |
| C/C | 54(74.0) | 19(26.0) | – | – | 1 | – |
| C/T | 42(57.5) | 31(42.5)[a] | 4.38 | 0.036 | 2.098 | 1.043–4.220 |
| T/T | 11(61.1) | 7(38.9) | 1.17 | 0.279 | 1.809 | 0.613–5.338 |
| C/T+T/T | 53(58.2) | 38(41.8)[a] | 4.42 | 0.036 | 2.038 | 1.044–3.976 |
| 399G/A polymorphism | | | | | | |
| G/G | 44(62.9) | 26(37.1) | – | – | 1 | – |
| G/A | 53(65.4) | 28(34.6) | 0.108 | 0.742 | 0.894 | 0.459–1.742 |
| A/A | 10(85.7) | 3(14.3)[b] | 0.954 | 0.528 | 0.508 | 0.128–2.015 |
| G/A+A/A | 63(67.0) | 31(33.0) | 0.307 | 0.58 | 0.833 | 0.436–1.592 |

[a]$P$<0.05, vs. C/C genotype. [b]The data was analyzed using Fisher's exact propability. Other footnotes as in Table 2.

**Table 4 Correlation of XRCC1 variable genotype combination with sensitivity to chemotherapy in NSCLC patients**

| Genotype | | The sensitivity to chemotherapy | | $P$ | OR | 95% CI |
|---|---|---|---|---|---|---|
| 194C/T polymorphism | 399G/A polymorphism | Ineffective [number (%)] | Effective [number (%)] | | | |
| not C/T | not G/G | 33(62.3) | 20(37.7) | | | |
| not C/T | G/G | 28(70.0) | 12(30.0) | | | |
| C/T | not G/G | 32 (4.4) | 11(25.6) | | | |
| C/T | G/G | 14(50.0) | 14(50.0)[a] | 0.063 | 2.163 | 0.949–4.932 |

[a]$P$>0.05, vs. other three genotypes. Abbreviations as in Table 2.

Table 5 Correlation of haplotype of XRCC1 codon 194 and codon 399 with sensitivity to chemotherapy in NSCLC patients

| Haplotype | Effective (%) | Ineffective (%) | $\chi^2$ | Pearson's P | Odds ratio (95% CI) |
|---|---|---|---|---|---|
| C G | 40.2 | 42.7 | 0.191 | 0.662 | 0.902(0.568-1.432) |
| C A | 18.6 | 29.3[a] | 4.470 | 0.035 | 0.551(0.316-0.962) |
| T G | 30.0 | 23.2 | 1.802 | 0.180 | 1.418(0.850-2.364) |
| T A | 11.3 | 4.9[a] | 4.636 | 0.031 | 2.486(1.061-5.829) |

[a]P<0.05, vs. other haplotype. Abbreviations as in Table 2.

## Discussion

Individualized cancer treatment includes treatments based on clinical factors and functional genomic and proteomic factors. The essence of individualized cancer treatment is functional genome-based individualized treatment. Gene polymorphisms affecting drug metabolic enzymes, protein transporting receptors, and other drug targets are important reasons for individual variations in response to drugs.

Currently, treatment for advanced stage NSCLC is primarily a chemotherapy-based integrated strategy, with NP as the most frequently used first-line regimen. Clinical studies have found that different patients with NSCLC respond differently to NP. Even with the same clinical stage, the same drug dosage, and other general factors, patients can still present different efficacy or adverse effects. Our study attempted to explain the variation in sensitivity to chemotherapy at the level of gene polymorphism. The results suggested that chemotherapeutic efficacy in patients with the C/T genotype in codon 194 of XRCC1 was significantly higher than those with the C/C genotype in codon 194. The efficacy for patients with the C/T+T/T genotype in codon 194 was also significantly higher as compared to those with the C/C genotype. In addition, we found that when compared to patients with other genotypes (31.4%), efficacy of chemotherapy further increased in patients with the C/T genotype on codon 194 and the G/G genotype on codon 399 (50.0%).

These findings suggested that the CT+TT genotype carriers in codon 194 of XRCC1 was more sensitive to NP than the CC genotype carriers. NP includes two drugs, vinorelbine and cisplatin, but currently no published literature has yet reported the correlation between the polymorphisms of XRCC1 and the efficacy of either drug. The body may develop resistance to vinorelbine by either 1) changing the binding sites to the drug or 2) arresting tumor cells in the $G_2$/M phase.[12] Currently the mechanisms underlying the resistance against platinum compounds are considered to be 1) reducing drug accumulation, 2) eliminating the cytotoxic effects of the drug by conjugation, 3) increasing the degeneration of DNA adducts induced by platinum compounds, or 4) increasing the ability to repair damaged DNA. Among these mechanisms, the ability to repair DNA is an influential factor for the efficacy of platinum compounds. As an important DNA-repairing gene, XRCC1 repairs DNA damage induced by a variety of factors, including oxidative stress by interacting with poly (ADP-ribose) polymerase, DNA ligase Ⅲ and DNA pylomerase β.[13] Some studies have reported that polymorphisms in XRCC1 affected the activity of XRCC1 proteins,[14] and thus affected its ability to repair DNA. In healthy individuals, such repairing activity reduces susceptibility to malignant tumors, whereas in patients with malignant tumors, such repairing activity decreases the sensitivity to drugs.

Our study suggests that individuals with the C/T and T/T genotypes in XRCC1 had increased sensitivity to chemotherapy. We believe that such variation in sensitivity to NP, which was reflected in the variation in polymorphisms of XRCC1, might be related to platinum compounds, rather than to vinorelbine. It was possible that the C→T mutation in the C26304T (Arg194Trp) polymorphism affected the activity of XRCC1 proteins and thus decreased its ability to repair DNA. Therefore the repairing activity on DNA damage induced by cisplatin was decreased, and the efficacy of the chemotherapy improved. That is, patients with a T allele in XRCC1 codon 194 might be more sensitive to platinum compounds and thus have increased sensitivity to chemotherapy.

Using haplotype as predictors of drug efficacy and genetic diagnosis has been a research hotspot in recent years. Haplotype means a group of correlated SNP sites on a certain region of the chromosome. Adjacent SNP sites tend to be inherited as a group. Haplotype includes genetic information in numerous SNP sites. In statistical analysis, haplotype produces better statistical results and has better practical implications than individual SNPs. Hirata *et al*. found that the T-A haplotype in codons 194 and 399 of XRCC1 was significantly more frequent in Japanese patients with prostate cancer.[15] By using SHEsis, our study conducted further haplotype analysis on 2 SNP sites of codon 194 and 399 in XRCC1, and revealed that the efficacy in patients with NSCLC with the T-A haplotype was significantly higher than those with other haplotypes ($P$=0.031), while the chemotherapeutic efficacy in patients with the C-A haplotype was lower ($P$=0.035), demonstrating that patients with a T allele on codon 194 of XRCC1 tended to have better efficacy with chemotherapy, while patients with a C allele tended to be less sensitive to chemotherapy. The results of haplotype analysis further confirmed that CT+TT genotype carriers on codon 194 of XRCC1 had increased sensitivity to chemotherapy than the CC genotype carriers when using NP.

Studies on the relationship between XRCC1 polymorphisms and chemotherapeutic efficacy have not taken regimen specificity into consideration,[6-10] whereas inconsistent chemotherapeutic interventions will probably interfere with the evaluation of the relationship between polymorphisms and treatment efficacy. Our study used NP as an inclusion criterion when screening patients. By ensuring consistent treatment across our study population, we

excluded the potential influence of drug variations on efficacy. The results of our study suggest that polymorphisms in codon 194 and 399 of XRCC1 were substantially valuable in predicting the efficacy of NP in treating patients with advanced stage NSCLC, and thus could provide evidence for selecting individualized treatment, particularly NP, in clinical practice.

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