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Relationship between DNA repair gene *XPD751* single-nucleotide polymorphisms and prognosis of colorectal cancer

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ABSTRACT. We examined the relationships between single-nucleotide polymorphisms (SNPs) in the DNA repair gene *XPD751* and the efficacy and time to disease progression (TTP) in colorectal cancer patients after platinum-based chemotherapy. Ninety-eight patients diagnosed with advanced colorectal cancer were subjected to oxaliplatin and 5-fluorouracil combination therapy. DNA was extracted from venous blood before chemotherapy. Polymerase chain reaction-restriction fragment length polymorphism analysis was used to detect *XPD751* SNPs. The relationship between genotypes and prognosis was compared. The frequencies of the *XPD751* Lys/Lys, Lys/Gln, and Gln/Gln genotypes were 76 (77.55%), 17 (17.35%), and 5 (5.10%), respectively. The efficiency of *XPD751* Lys/Lys, Lys/Gln and Gln/Gln genotypes were 50.00, 29.41, and 20%, respectively. The efficiency rate between *XPD751* Lys/Lys and Lys/Gln showed a significant difference ($\chi^2 = 4.04$, $P < 0.05$). After adjusting for gender, age, and metastasis location, chemotherapy failure in patients carrying *XPD751* Lys/Gln was 3.404-fold higher than in patients carrying the Lys/Lys genotype. Median TTP was 304 days (10.1 months) and median TTP in patients with *XPD751* Lys/Lys and ≥1 Gln genotype was 340 and 87 days. After comparing TTP in patients carrying Lys/Lys and

patients carrying ≥1 Gln, the difference was significant. SNPs in the DNA repair gene *XPD751* may be associated with oxaliplatin and 5-fluorouracil chemotherapy sensitivity in colorectal cancer patients. These polymorphisms may be associated with TTP in patients with advanced colorectal cancer after first-line chemotherapy of oxaliplatin. *XPD751* SNPs may be predictive factors of prognosis in colorectal cancer patients receiving oxaliplatin and 5-fluorouracil chemotherapy.

Key words: Colorectal cancer; Disease progression time; Drug efficacy; Repair genes; *XPD751*

INTRODUCTION

Colorectal cancer (CRC) is a common gastrointestinal cancer, and CRC mortality has increased in the urban and rural areas of China (Chen et al., 2006). With diet and lifestyle changes, CRC incidence and mortality is expected to continue to increase in China to become one of the most prevalent types of cancer (Zhen and Cai, 2004). Thus, it is very important to understand the pathogenesis and improve treatment of colorectal cancer. The xeroderma pigmentosum (XPD) gene is associated with nucleotide excision repair (NER) functional changes, which may affect the efficacy and prognosis of platinum chemotherapy. The incidence of CRC in our country is increasing at an average annual growth rate of 4.2%, making it a serious threat to human health. Chemotherapy plays an important role in the comprehensive treatment of CRC. An oxaliplatin and FOLFOX regimen consisting of 5-fluorouracil (5-Fu) is currently the most preferred chemotherapy regimen for CRC treatment (Sun et al., 2007). Studies have shown that single-nucleotide polymorphisms in the human DNA repair gene *XPD751* are associated with the sensitivity of platinum drugs (Gurubhagavatula et al., 2004). However, in different CRC patients receiving the same chemotherapy regimen, the efficacy and tolerability of treatment, disease progression time, and survival time show large differences. These differences cannot be explained with regards to age, concomitant diseases, concomitant medications, liver and kidney function status, and other factors. DNA damage repair, drug metabolism, and detoxification gene polymorphisms affect the sensitivity and toxicity of drugs in different individuals. Studies have shown that low levels of DNA damage repair in tumor tissue can reduce platinum drug and DNA adduct resection as well as enhance chemosensitivity, which may improve the prognosis of platinum-based chemotherapy (Quintela-Fandino et al., 2006). NER is the key process in DNA repair, and *XPD751* plays an important role in this pathway by affecting the sensitivity of tumor cells to platinum drugs. Single-nucleotide polymorphisms (SNPs) can be used to predict prognosis in patients receiving platinum-based chemotherapy. SNPs have varying effects in different races. In this study, we examined the relationship between these polymorphisms and treatment efficacy and time to disease progression (TTP) in Chinese patients with advanced CRC receiving the platinum-based chemotherapy.

MATERIAL AND METHODS

Subjects

From 2005-2010, 98 patients with advanced CRC who received pathological diagno-

sis and therapy in our hospital were collected. DNA was extracted from venous blood; 60 cases were male and 38 cases were female. They were aged from 42-74 years with a median age of 57 years. Fifty-five cases had colon cancer and 43 cases had CRC. A total of 33 cases had liver metastasis, 20 cases had liver metastasis and abdominal lymph node metastasis, 12 cases had liver and lung metastases, 8 cases had lung metastasis, 18 cases had abdominal lymph node metastasis, and 7 cases had abdominal lymph node metastasis and ascites. All cases selected were confirmed by computed tomography or magnetic resonance imaging scanning to measure lesion diameter, which was greater than 10 mm. Before chemotherapy, routine blood tests and liver and kidney functions were normal. There were no significant electrocardiogram abnormalities and Karnofskyp scores were all greater than 70 points.

Chemotherapy

All enrolled patients were given FOLFOX chemotherapy, which included 85 mg/m^2 d_1 oxaliplatin, 200 mg/m^2 d_{1-2} leucovorin (CF), 400 mg/m^2 d_{1-2} 5-Fu for ivgtt, 600 mg /m^2 d_{1-2} 5-Fu for 22-h continuous infusion. Each treatment cycle was 2 weeks.

Efficacy evaluation and outcome measurements

DNA was extracted from 98 subjects who had completed 4-6 cycles of chemotherapy, and efficacy evaluation was performed. TTP was observed from the start of chemotherapy until the first confirmed disease progression or death; 16 patients did not show TTP until the end of the follow-up and these data were censored.

Specimen collection and experimental methods

Before chemotherapy, 2 mL peripheral venous blood was taken from all patients. After sodium citrate anticoagulation treatment, the samples were stored at -20°C. DNA was extracted from anticoagulated blood using a DNA extraction kit from Beijing Baitaike Biotechnology Co., Ltd. (Beijing, China). The polymerase chain reaction (PCR)-restriction fragment length polymorphism technique was used to amplify the DNA repair gene *XPD751*, containing Lys751Gln polymorphic gene fragment (436-bp), and the following primers for *XPD751* were used for detection: 5'-GCCCGCTCTGGATTATACG-3' and 5'-CTATCATCTCCTGGC CCCC-3'. The 25-μL PCR system contained 5 μL template DNA, 10 pmol of each primer, 1 μL dNTPs, 0.2 μL ExTaq polymerase, 2.5 μL 10X PCR buffer, 1.5 μL $MgCl_2$. The PCR conditions were 94°C denaturing for 2 min, 94°C for 30 s, 62°C for 30 s, and 72°C for 30 s. After 35 cycles, amplified products were extended for 7 min at 72°C. Next, 5 μL PCR product was digested with the restriction enzyme *Pst* at 37°C overnight, and 3% agarose gel electrophoresis analysis was performed to detect the *XPD751* genotypes. All reagents and primers were purchased from Takara Bio (Shiga, Japan). DNA markers were purchased from Brad Company (Yeh et al., 2005). The results are shown in Figure 1.

Wild-type 751 Lys/Lys PCR products contained 1 *Pst* restriction site, generating 2 fragments of 290 and 146 bp. Two restriction sites were generated after Lys→Gln mutation, and the homozygous mutant Gln/Gln produced 3 fragments of 227, 146, and 63 bp. The heterozygous mutant Lys/Gln produced 4 fragments of 90, 227, 146, and 63 bp.

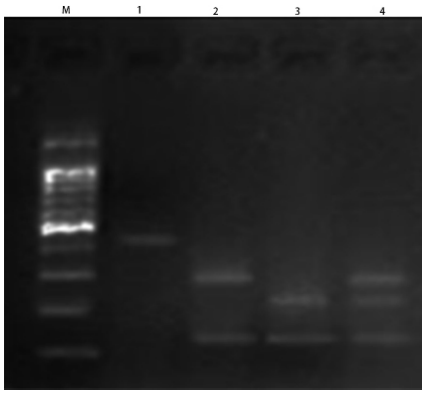

Figure 1. Lys751Gln PCR products of the XPD gene and electrophoresis patterns after *Pst*I digestion. (Note: *lane M* = Marker; *lane 1* = 436-bp fragment; *lane 2* = Lys/Lys genotype (A/A); *lane 3* = Gln/Gln genotype (C/C); *lane 4* = Lys/Gln genotype (A/C).

Statistical methods

The SPSS 17.0 statistical software was used for statistical analysis (SPSS, Inc., Chicago, IL, USA), while the χ^2 test was used to detect the chemotherapy genotypes differences in the DNA repair gene *XPD751*. The unconditional logistic regression model was used to calculate the odds ratio (OR) and 95% confidence intervals (95%CI) to indicate chemosensitivity differences among different genotypes. All tests were 2-sided, and $P < 0.05$ was considered to be statistically significant. MTTP was calculated using the Kaplan-Meier method. Log-rank test was used to compare MTTP among different genotypes. Cox proportional hazards model was used to assess the impact of various factors affecting the results of the experiment and the 95%CI was calculated. All P values were 2-tailed, and $P < 0.05$ was considered to be statistically significant.

Evaluation criteria of chemotherapy efficacy

The evaluation criteria were based on the recent RECIST objective efficacy evaluation of solid tumors, divided into complete remission (CR), partial remission (PR), stable (SD) and progression (PD), and the CR + PR were considered effective (RR). Evaluation included the following: 1) CR of target lesion: disappearance of all target lesions. PR: Sum of the baseline lesion diameter narrowing reached 30%. PD: Total increase of baseline lesion diameter was more than 20% or new lesions. SD: Total lesion diameter baseline shrank but did not reach PR or increased but did not reach PD. 2) Evaluation of non-target lesion: CR: All non-target lesions disappeared and tumor marker levels were normal. SD: One or more non-target lesions and/or tumor markers persisted or were higher than normal levels. PD: One or more new lesions and/or non-target lesions progression.

RESULTS

SNP distribution in DNA repair genes XPD751

The genotype frequencies in the DNA repair gene *XPD751* were: 76 with Lys/Lys

(77.55%), 17 with Lys/Gln, and 5 with Gln/Gln (22.45%).

Association between the DNA repair gene *XPD751* SNPs and chemotherapy efficacy

Complete remission was not observed in any of the 98 patients, 0 cases had CR, 44 cases had PR (44.90%), 34 cases had SD (34.70%), and 20 cases had PD (20.41%). The effective rate of those carrying *XPD751* Lys/Lys was 50.00%, while the effective rate carrying Lys/Gln was 29.41% and the effective rate carrying Gln/Gln was 20.00%. Patients were divided into groups according to treatment effectiveness (CR + PR). The chemotherapy effectiveness rates for the *XPD751* A/A, A/C, and C/C genotypes were 38 patients (50%), 5 cases (29.41%), and 1 case (20.00%), respectively. The frequency of genotype Gln/Gln was low in China (8, 20, 22), and the number of cases collected in this study was limited. Therefore, the expression of the Gln/Gln genotype was rare. This experiment only found that there were differences between the efficiency of Lys/Lys and Lys/Gln, and that these differences were significant ($\chi^2 = 4.04$, $P < 0.05$), as shown in Table 1. In logistic regression, after adjusting for gender, age, and other factors in this group of patients, the *XPD751* genotype remained significantly associated with chemosensitivity ($P < 0.05$), and the OR = 3.404 suggested that individual chemosensitivity in patients carrying the A/A genotype was 3.404-fold higher than in patient carrying the A/C genotype in the *XPD751* codon (95%CI = 1.819-6.369; Table 2 and 3).

Table 1. Association between *XPD751* SNPs and efficacy of chemotherapy in 98 cases of advanced colorectal cancer (N = 98 patients).

Genotype	CR	PR	SD	PD	n	χ^2	P value
Lys/Lys	0	38	26	12	76		
Lys/Gln	0	5	6	6	17	4.04	<0.05
Gln/Gln	0	1	2	2	5		

Table 2. Characteristics of patients and comparison of efficacy (N = 98).

	CR+PR	SD	PD	N	χ^2	P value
Gender						
Man	27	21	12	60	0.011	0.917
Female	17	13	8	38		
Age (years)						
<57	20	15	14	49	4.257	0.039
>57	24	20	5	49		
Tumor metastasis						
Liver metastases	18	11	4	33	9.397	0.094
Liver metastasis with abdominal lymph node metastasis	10	8	2	20		
Liver metastasis with pulmonary metastasis	5	4	3	12		
Lung metastases	4	3	1	8		
Abdominal lymph node metastasis	5	6	7	18		
Abdominal lymph node metastasis with ascites	2	2	3	7		
Genotype						
Lys/Lys	38	26	12	76		
Lys/Gln	5	6	6	17	5.831	0.016
Gln/Gln	1	2	2	5		

Table 3. Association between *XPD751* polymorphisms and median TTP.

Genotype	MTTP (95%CI, day)	Log-rank test		Cox regression		P
		χ^2	P	OR	95%CI	
Lys/Lys	340 (306.979-373.235)	21.089	<0.05	3.404	(1.819-6.369)	<0.05
Lys/Gln or Gln/Gln	87 (71.652-102.348)					
Total	304 (280.610-327.390)					

Prognosis status in different *XPD751* genotypes

The median follow-up time for the 98 patients was 480 (90-1200) days. Post-treatment median TTP was 304 days (10.1 months). The median TTPs for different genotypes were compared; the *XPD751* Lys/Lys gene frequency included 76 cases (77.55%), with a median TTP of 340 days (11.3 months). The genotype frequency of Lys/Gln and Gln/Gln was 22 (22.45%), with a median TTP of 87 days (2.9 months). The median TTP between Lys/Lys and patients with at least 1 Gln was statistically significant ($\chi^2 = 21.089$, $P < 0.05$), suggesting that oxaliplatin shows better prognosis in patients with the Lys/Lys genotype (Table 3 and Figure 2).

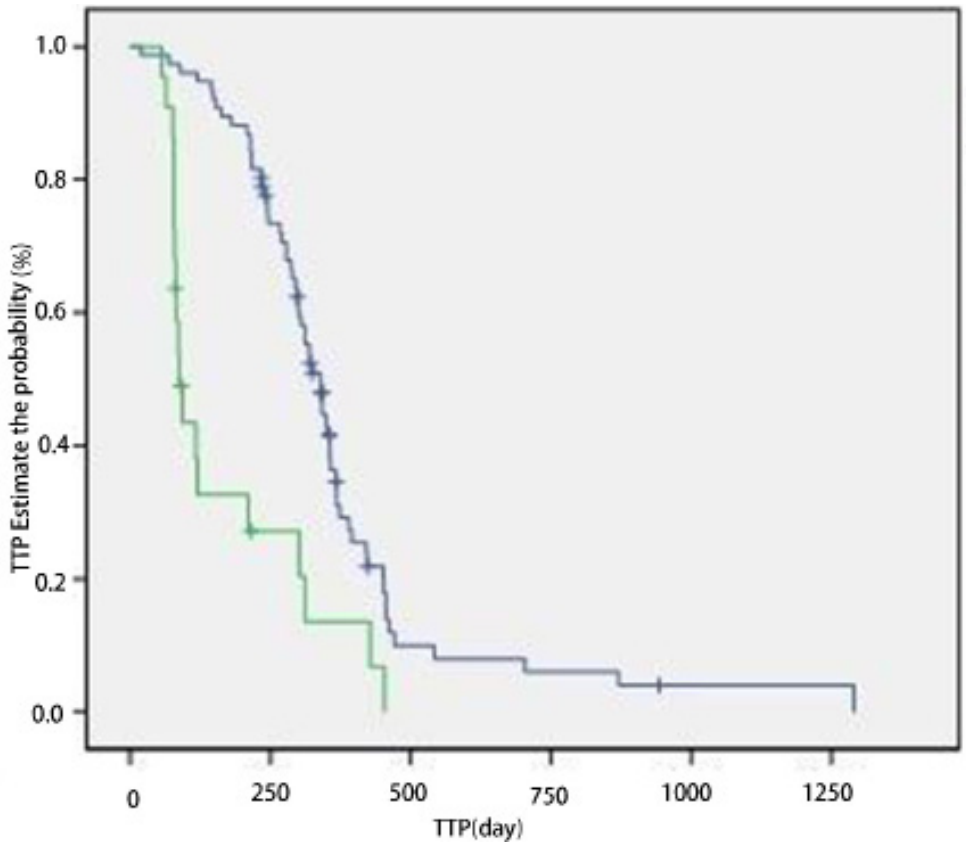

Figure 2. Association between XPD polymorphisms and median TTP.

DISCUSSION

The NER system is an important component of the human DNA repair system, and platinum-induced DNA damage is typically repaired by this system. Cytotoxicity of platinum drugs to tumor cells occurs through binding the nucleophilic cell DNA to form platinum-DNA adducts, leading to crosslinking within the chain-stranded DNA and inducing DNA damage and cell death. This can affect the body's sensitivity to platinum-based chemotherapy. Thus, differences in DNA damage repair capacity may be an important factor determining platinum drug efficacy (Rosell et al., 2002; Guo et al., 2009). The *XPD* gene is an important member of the NER system and is located on the long arm of chromosome 19. It is mainly involved in NER and transcription, identification, and repair of a wide range of damage unrelated to gene structure; it can also remove a variety of types of DNA damage in the body. Amino acid sequence changes may affect the interactions between different proteins, leading to individual differences in repair capacity (Matullo et al., 2001). The *XPD*-encoded protein is ATP-dependent evolutionary conserved DNA helicase, an important component of the type II transcription factor H composite (TFIIH), which participates in NER and gene transcription. The mutation frequency of codons 312 and 751 in the *XPD* gene were high. Asp312Asn (G→A) and Lys751Gln (A→C) were intentional mutation causing amino acid changes and affecting the function of DNA repair pathways. Asp312Asn is highly conserved in evolution and may play a role in maintaining XPD protein function. Lys751Gln is located at the N-terminus of the XPD protein and is not well-conserved, and thus can be used as an indicator of DNA repair capacity.

A previous study confirmed that the codon 751 C→A polymorphism in *XPD* may cause the amino acid substitution Lys751→Gln751, which was closely associated with individual repair differences. This can increase the incidence and risk of cancer and affect tumor sensitivity to anti-cancer drugs as well as the prognosis of patients (Zárate et al., 2006). A study by Paré et al. (2008) found that *XPD751* SNPs affected the prognosis of patients with advanced CRC receiving oxaliplatin treatment. The progression-free survival time in patients with the Lys/Lys genotype was 12 months, while the median progression-free survival was 8 months in patients with the Lys/Gln and Gyn/Gln genotypes. For median overall survival, the difference was also significant, and the median overall survival in patients with the A/A genotype was 41 months; the median overall survival for patients with the other 2 genotypes was 17 months, and this difference was statistically significant. Le Morvan et al. (2007) observed similar results; event-free survival differed in for different *XPD751* genotypes, and the median event-free survival and overall survival in patients carrying at least 1 mutant allele was shorter than that in patients carrying the wild-type genotype. Park et al. (2001) found that in 73 CRC patients with metastatic joint treatment with 5-Fu and oxaliplatin, patients carrying the *XPD751* Lys/Lys genotype had a median survival of 17.4 months, while the median survival time of patients with the Lys/Gln and Gln/Gln genotypes was 12.8 and 3.3 months, respectively; this difference was significant. The prognosis of patients with SNPs in the *XPD312* gene showed no difference. Most previous studies are consistent with our results, and the survival time in patients carrying the wild-type allele of *XPD751* was longer than that in patients carrying a mutation of any allele. The present study showed that patients carrying the *XPD751* Lys/Lys genotype were more likely to have an increased risk of lung cancer and were more sensitive to chemotherapy. Chen et al. (2002) found that the *XPD751* Lys gene was positively correlated with lung cancer risk. Lunn et al. (2000) reported that the *XPD751* Lys/Lys genotype can increase the level of chromosomal aberrations and reduce the ability to repair DNA

damage. The Spanish Lung Cancer Collaborative Group found that in 52 patients with phase IV lung cancer receiving platinum-based chemotherapy, the median TTP for those with the *XPD751* Lys/Lys genotype was longer, and survival was poor in patients carrying the Gln/Gln genotype (Viñolas et al., 2003). It has been hypothesized that patients carrying the *XPD751* Gln allele had low DNA repair capacity (Hemminki et al., 2001; Spitz et al., 2001; Au et al., 2003). Yin et al. (2006) showed that lung cancer risk in non-smoking women carrying the *XPD751* Lys/Gln or Gln/Gln genotype was 2.80-fold higher than that in non-smoking women carrying the Lys/Lys genotype. Sarries et al. (2003) reported that patients carrying the *XPD751* Lys/Gln genotype had the best prognosis when receiving gemcitabine/cisplatin chemotherapy, the prognosis for the Lys/Lys was acceptable, while the prognosis for Gln/Gln was the worst.

We found that in 98 advanced CRC patients receiving FOLFOX chemotherapy, the objective response rates in patients carrying the *XPD751* Lys/Lys and Lys/Gln genotypes were 50.00 and 29.41%, respectively. The possibility of chemotherapy failure in patients carrying the XPD751 Lys/Gln genotype was 3.404-fold higher than that in patients carrying the Lys/Lys genotype. The median TTP in patients carrying the Lys/Lys genotype was 340 days (11.3 months), which was significantly higher than that in patients carrying the *XPD751* Lys/Gln or Gln/Gln genotype, with a median TTP of 87 days (2.9 months) ($\chi^2 = 21.089$, $P < 0.05$). Patients carrying the *XPD751* Lys/Lys genotype were more sensitive to platinum-based chemotherapy, and the median TTP was longer, which is consistent with the results of a previous study (Lou et al., 2006). SNPs in DNA repair genes affect the sensitivity to the drugs in different individuals. Gender, age, and metastasis sites were not significantly associated with prognosis, but SNPs in the DNA repair gene *XPD751* were associated with chemotherapy prognosis of CRC patients receiving FOLFOX. The prognosis for patients with the wild-type genotype was better. The results of the present study were not completely consistent, which may be due to ethnicity, lifestyle, environmental factors, and various family hereditary diseases; tumor sensitivity to chemotherapy may be affected by the interaction of multi factors. Therefore, multi-gene studies are more suitable for evaluating the selection and prognosis of chemotherapy.

With the standardization of detection technology and testing, detecting SNPs in the peripheral blood DNA repair gene *XPD751* may be useful for predicting the sensitivity to chemotherapeutic drugs and disease progression time in different CRC patients. These methods may also provide a basis for individualized treatment of CRC patients.

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