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Original Article

DNA repair gene XPG C46T polymorphism predicts response to platinum-based neoadjuvant chemoradiotherapy and prognosis in clinical stage II/III rectal cancer patients

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Abstract: The aim of this study was to investigate the predictive role of XPG C46T (rs1047768) gene polymorphism on response to neoadjuvant chemoradiotherapy (XELOXART Trial) and prognosis in Chinese clinical stage II/III rectal cancer patients. A total of 180 patients diagnosed with clinical stage II/III rectal cancer received XELOXART Trial was enrolled in this study. XPG C46T was genotyped by the Taqman real-time polymerase chain reaction (PCR), and was assessed for correlation with clinical variables, tumor response, disease free survival (DFS), and overall survival (OS). The Cox proportional hazards model was used to determine independent factors contributing to OS. Concerning the XPG C46T polymorphism, the C/C genotype was significantly associated with pathologic response to XELOXART Trial and better outcomes (DFS and OS) ($P < 0.05$), while the C/T genotype and T/T genotype could not provide any predictive information. The Cox proportional hazards model indicated that CT stage [$P < 0.05$, hazard ratio (HR) = 2.33, 95% CI = 1.06-3.52], CN stage ($P < 0.05$, HR = 4.25, 95% CI = 2.13-8.49) and XPG C46T polymorphism ($P < 0.05$, HR = 2.40, 95% CI = 1.67-3.45) were independent factors in predicting OS. In conclusion, our study found that XPG C46T C/C is associated with response to XELOXART Trial and prognosis in clinical stage II/III rectal cancer received XELOXART Trial. Additional well-designed, large sample, multicenter, prospective studies are needed to confirm the result of this study.

Keywords: Rectal cancer, XPG C46T gene, polymorphism, neoadjuvant chemoradiation therapy, prognosis

Introduction

Rectal cancer is one of the leading causes of cancer-related deaths in the world [1]. Although advanced treatment, most of affected patients present metastatic disease and advanced cancer when they are diagnosed. For advanced rectal cancer patients, platinum-based neoadjuvant chemoradiotherapy (NCRT) is used as the standard first-line preoperative treatment [2]. A platinum compound exerts its cytotoxic effect by forming DNA adducts that inhibit DNA replication and consequently lead to cell apoptosis [3]. Platinum-based NRCTfor rectal cancer patients have been considered the optimal management strategy because of increased control of local disease, decreased toxicity rates, greater sphincter preservation rates, improved disease-free survival (DFS) and overall survival (OS) [4, 5]. However, despite these improvements, treatment for rectal cancer is associated with substantial morbidity, and the tumor responses to this regimen cover a wide spectrum, ranging from none to complete [6]. Therefore, an effective biomarker is urgently needed to identify the subgroup of patients who are poor responders to extensive long-course chemo-radiation to avoid unnecessary toxicity.

The clinical response to NRCT is influenced by multiple factors, including genetic and environmental factors [7]. Recently, many studies have shown that single nucleotide polymorphisms (SNPs) influence the mechanisms of DNA repair function, and have a role of removing DNA adducts [8-10]. Therefore, the polymorphisms

in SNPs might affect the response to platinum-based neoadjuvant chemoradiotherapy.

The ERCC5 gene, also known as xeroderma pigmentosum group G (XPG), is one of the essential DNA repair enzymes of the nucleotide excision repair (NER) pathway. This protein combined with ERCC1 is involved in a dual incision at both the 3' and 5' sites of the lesion, and produces the excision of damage-containing oligomers of 22-32 nucleotides in length. Currently, several studies suggested that XPG C46T (rs1047768) polymorphisms have a vital role in predicting response to platinum-based neoadjuvant therapy in several cancers, such as lung cancer and bone malignant tumors [7, 11]. However, its predictive value in advance rectal cancer is still largely unclear. In this study, we hypothesized that tagSNPs in the XPG C46T (rs1047768) may contribute toward rectal cancer patients' response to platinum agents. Therefore, we attempted to examine the association between tagSNPs in the XPG C46T (rs1047768) and a combination of preoperative radiotherapy and concurrent capecitabine plus oxaliplatin (XELOXART Trial) response in patients with clinical stage II/III rectal cancer.

Materials and methods

Patients and clinical assessment

This study was approved by the Research Ethics Committee of the Affiliated Cancer Hospital of Guangxi Medical University in China. One hundred-eighty patients were enrolled in this study. These patients were diagnosis as clinical stage II/III rectal cancer patients by pathological examination. The TNM stages were reported according to the American Joint Committee on Cancer (AJCC) [12]. Written informed consent was obtained from all the patients.

Genotyping

Genomic DNA was obtained from peripheral blood using a Qiagen Blood Kit (Qiagen, Chastworth, CA). Probes and primers were designed by Primer 5.0 software. The primers for XPGC46T (rs1047768) were 5'-ATTGAAGTTGTGAGGATGAAGAG-3' and 5'-GCCGATGAAACAAAGTGAGA-3'. The genotyping of SNPs were conducted using the Taqman real-time polymerase chain reaction (PCR) method with a 7900 HT sequence detector system (Applied Biosystems, Foster City, CA). The PCR reactions were conducted in a reaction of 30 μL solution of 10 pmol primer and 50 ng genomic DNA. The PCR reaction started at 95°C for 5 minutes, denatured at 95°C for 30 s, annealed at 67.5°C for 45 s and extended at 72°C for 360 s. A total of 40 cycles were performed. For quality control, a minimum of 10% of DNA samples were randomly selected and were genotyped again to confirm the results. The results confirmed 100% concordance.

Multimodal treatment

The XELOXART regimen was carried on in all patients, according to the NCCN guideline [13]. Radiotherapy consisted of 5000 cGy delivered in 25 fractions of 200 cGy five times per week. The iliac lymphatic drainage areas, the surrounding intestines and the tumor bed were considered as target field. 50 mg/m^2 oxaliplatin was given on the first day, and 850 mg/m^2 capecitabine bid was given for 5 days during the first, second, fourth and fifth weeks of radiotherapy. Within 5-6 weeks after the completion of the XELOXART regimen, low-anterior resection or abdominoperineal resection was scheduled according to the tumor location. Surgery was done by experience surgeon and the principle of TME was strictly followed. Four weeks after surgery, the patients received four more cycles of chemotherapy consisting of 130 mg/m^2 oxaliplatin on day 1 and 1000 mg/m^2 capecitabine bid on day 1 to day 14. The postoperative regimens were repeated every 3 weeks.

Assessment of NCRT effects

According to the tumor regression grade (TRG), which was assessed on the resected surgical rectal carcinoma, the response to preoperative chemo-radiotherapy was assessed after 4 weeks of treatment. We used the tumor regression grade (TRG) system descripted by Dworak et al. to access tumor response [14]: The TRG ranges from TRG0 when no fibrosis is visible (no regression), to TRG4 when no viable tumor cells are detected (complete response). Tumor regression grade 1 = dominant tumor mass and obvious fibrosis or mucin; TRG2 = dominantly fibrotic or mucinous changes, with few tumor cells or groups; and TRG3 = very few tumor cells in fibrotic or mucinous tissue. Patients

Table 1. Correlations between clinicopathological parameters and tumor response in clinical stage II/III rectal cancer patients

Clinicopathological parameters	N	TNM		*P*-value	TRG		*P*-value
		Downstaging (n)	Non-downstaging (n)		Major response (n)	Poor response (n)	
Age (years)							
> 60	78	41	37	0.76	36	42	0.89
≤ 60	102	56	46		46	56	
Gender							
Male	98	53	45	0.96	44	54	0.85
Female	82	44	38		38	44	
Histology							
Differentiated	85	48	37	0.51	37	48	0.61
Undifferentiated	95	49	46		45	50	
Distance from anal verge							
> 6 cm	108	61	47	0.39	48	60	0.71
≤ 6 cm	72	36	36		34	38	
CT stage							
3	101	57	44	0.44	49	52	0.37
4	79	40	39		33	46	
CN stage							
Positive	87	47	40	0.68	37	50	0.43
Negative	93	50	43		45	48	
XPG C46T polymorphism							
C/C genotype	79	54	25	< 0.05	49	30	< 0.05
C/T genotype	56	28	28		21	35	
T/T genotype	36	15	30		11	25	

Note: TRG, tumor regression grade.

with TRG0 or 1 were defined as nonresponders, whereas those with TRG2, -3, or -4 were classified as responders. All tumors were classified by the same trained pathologist who had no access to patient data and clinical status.

Follow-up

All rectal cancer patients were underwent a systematic follow-up, including physical examinations such as serum level of carcinoembryonic antigen, chest X-ray every 3 months, abdominal and pelvic CT or MRI every 3 months, and colonoscopy within every 6 months after treatment. DFS and OS in these patients were also evaluated.

Statistical analysis

The primary endpoint of this study was the pathologic response to NCRT. The second point of interest was the patient outcome with the DFS and OS. To determine the ability of clinicopathological parameters (age, gender, cT, cN, differentiation, and distance from anal verge et al.) to predict tumor response to XELOXART trail, Pearson's chi-square test was used. The impact of the XPG C46T genotype on DFS and OS was determined using the Kaplan-Meier method. To assess the association between each clinic-pathological parameter and OS, univariate statistical analyses were performed; moreover, multivariate analyses were carried out using logistic or Cox regression with stepwise procedure. Odds and hazard ratios with 95% confidence intervals are presented. All statistical analysis was performed with the Statistical Package for the Social Sciences, version 16.0 (SPSS 16.0), with a $P < 0.05$ considered to be significant.

Results

The characteristic of the 180 patients were listed in **Table 1**. Overall, there were 98 male and 82 female involved in this study. Seventy

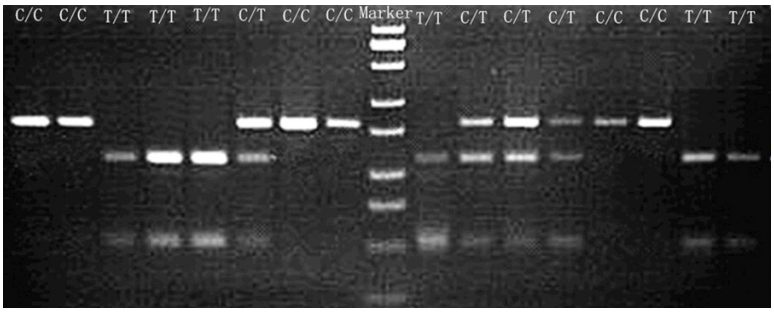

Figure 1. Detection of the XPG C46T polymorphism by polymerase chain reaction-restriction fragment length polymorphism.

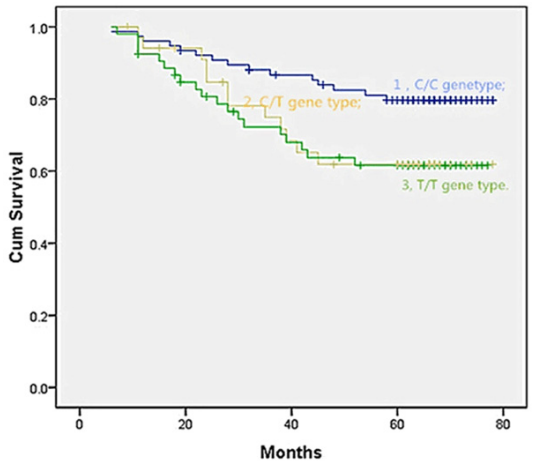

Figure 2. Kaplan-Meier curves for disease free survival in rectal cancer according to the XPG C46T genotype.

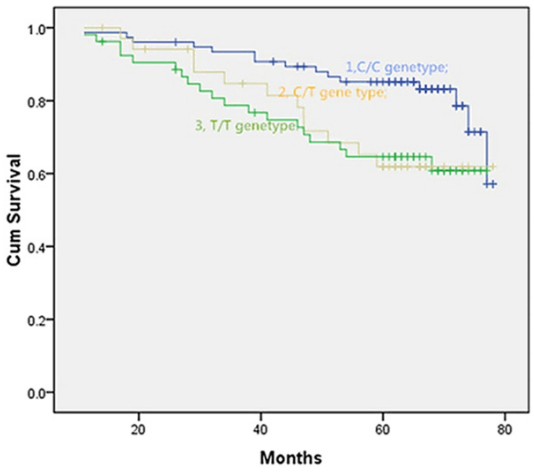

Figure 3. Kaplan-Meier curves for overall survival in rectal cancer according to the XPG C46T genotype.

eight of the patients were more than 60 years old, the rest of them were younger than 60 years. Nighty-three patients were clinically assessed as stage II, and 87 patients were clinically assessed as stage III. One hundred and eight tumors were localized in more than 6 cm above the anal verge with rest of which localized in lower 6 cm above the anal verge. Eighty-five of the histological tumors were differentiated, and 95 of which were undifferentiated.

XPG C46T (rs1047768) genotyping

Genotyping for XPG C46T (rs1047768) was successful in 171 (95%) of 180 cases. In 9 patients (5%) genotyping was not successful because of limited quantity and quality of extracted genomic DNA or biopsy samples. Forty-six percent (79/171) of patients were homozygous for C/C allele, 33% (56/171) were heterozygous C/T, and 21% (36/171) were homozygous for the T/T allele (**Figure 1**).

Association between clinicopathological parameters and response to NCRT

Among the 171 patients whose XPG C46T (rs1047768) genotype were successful obtained, eighty one (47.37%) patients were good responders, with 34, 35, and 12 patients evaluated as TRG2, TRG3, and TRG4, respectively. Nighty (52.63%) cases were non-responders, with 14 patients displaying no regression at all (TRG0) and 76 presenting a poor tumor regression (TRG1).

Associations between the pathologic response to NCRT and patient characteristics were analyzed by using Pearson's chi-square test. No statistical significance was found between the pathologic response and classical clinicopathologic parameters such as age, gender, tumor location, histology, distance from anal verge, CT stage, and CN stage ($P > 0.05$), but the association was found between pathologic response and XPG C46T (rs1047768) genotype ($P < 0.05$). Patients harboring the C/C variant for the rs1047768 polymorphism were significantly associated with a good tumor regression ($p < 0.05$; **Table 1**). Indeed, 62% (49 of 79) of TRG-evaluable patients harboring the C/C genotype were good responders, compared with 37.5%

Table 2. Univariate and Multivariate Proportional Hazards Models for Overall Survival

Prognostic Variable	Univariate Model			Multivariate Model		
	Hazard ratio	95% CI	*P*-value	Hazard ratio	95% CI	*P*-value
Age (years)						
> 60 vs. ≤ 60	1.39	0.76-2.54	0.29	0.94	0.50-1.76	0.84
Gender						
Male vs. female	1.40	0.78-2.49	0.26	1.12	0.62-2.04	0.71
Histology						
Differentiated vs. Undifferentiated	1.97	1.08-3.58	< 0.05	1.42	0.76-2.67	0.27
Distance from anal verge						
> 6 cm vs. ≤ 6 cm	1.41	0.79-2.52	0.24	1.09	0.60-1.99	0.78
CT stage						
T3 vs. T4	2.15	1.19-3.86	< 0.05	2.33	1.06-3.52	< 0.05
CN stage						
Positive vs. Negative	3.38	1.78-6.43	< 0.05	4.25	2.13-8.49	< 0.05
XPG C46T polymorphism						
C/C vs. C/T vs. T/T	2.00	1.40-2.85	< 0.05	2.40	1.67-3.45	< 0.05

(21 of 56) and 30.6% (11 of 36) of patients having the C/T and T/T genotypes, respectively.

Association between XPG C46T (rs1047768) polymorphism and patients' outcome

The follow-up end up at June 30, 2014. Among the 171 patients who were successfully genotyped, six of them lost follow-up, remaining the 164 patients for evaluating the DFS and OS. In the whole group of these patients, one hundred and eighteen patients were alive (71.95%), the rest of them were died of disease recurrence and metastasis. The mean DFS was 52.54 ± 21.43 months and the mean survival was 57.12 ± 17.90 months. The 5-year DFS of patients with C/C allele was significantly longer than that of patients with C/T allele or T/T allele. ($P < 0.05$) (**Figure 2**). In the total study population, C/C allele patients had significantly better OS as compared with C/T allele or T/T allele patients ($P < 0.05$) (**Figure 3**).

Association between clinicopathological parameters and OS

Univariate analysis showed that histology, CT stage, CN stage and XPG C46T polymorphism were the factors associated with OS, however, a multivariate analysis showed that CT stage [$P < 0.05$, hazard ratio (HR) = 2.33, 95% CI = 1.06-3.52], CN stage ($P < 0.05$, HR = 4.25, 95% CI = 2.13-8.49) and XPG C46T polymorphism ($P < 0.05$, HR = 2.40, 95% CI = 1.67-3.45) were associated with the OS (**Table 2**).

Discussion

Oxaliplatin-based chemoradiotherapy was well established to influence the outcome for the cancer patients, and has been shown to be effective in the treatment of rectal cancer [15, 16]. However, these patients showed considerably different clinical outcomes even with the same pathological type, clinical stage, and treatment, suggesting that genetics may be an important determinant of this variable response. Thus, there is a huge demand for biomarkers to predict chemotherapy response and clinical outcome in the management of advance rectal patients. XPG C46T rs1047768 has been linked with the clinical outcome of several solid tumor, but no published study has examined the association of rs1047768 polymorphisms with the efficacy of chemoradiotherapy in patients with rectal cancer. In this study, we found that the rs1047768 variant C/C genotype significantly improved the treatment response in advanced rectal cancer patients, and associated with better DFS and OS.

The XPG gene has been mapped to chromosome 13q33 and consisted of 15 exons spanning ~30 kb of genomic DNA, and this kind of gene participates in two incision steps to correct the excision repair deficiency [17]. During the NER pathway, the XPG has a role of making one of the incisions required to excise a damaged oligonucleotide through cleaving 3' to DNA damaged site, and it also stabilizes the

DNA repair complex to damaged DNA [18]. Increased removal of platinum-DNA adducts by NER has been reported to be associated with cisplatin resistance [19-21]. In other words, individual response to platinum might be inversely correlated with NER capability [18].

In a previous study, the relation of rs1047768 polymorphisms and cisplatin response was examined in osteosarcoma [7], and the authors reported an association between the rs1047-768 variant TT genotype and better cisplatin response, and showed a significantly longer progress free survival (16.8 months) and OS (21.4 months) than CC genotype, with HRs (95% CI) of 0.31 (0.10-0.93) and 0.32 (0.06-0.97), respectively. Meanwhile, Zhang et al. found patients carrying rs1057768 TT genotype had a significantly lower treatment response to platinum drug therapy in lung cancer, and showed a significantly short median OS [11]. In patients with ovarian cancer treated with platinum-based chemotherapy, a shorter OS was reported for homozygous mutant [22]. For advanced colorectal cancer, Monzo et al. reported that polymorphism in XPG combined with XPA may be an important prognosticator of clinical outcome following oxaliplatin/fluoropyrimidine chemotherapy [23]. Kweekel et al. in their retrospective analysis suggested that the rs1047768 allele could be a marker for therapy resistance in patients treated with adjuvant chemotherapy [24]. In our series, the C/C genotype was significantly associated with a good response to neoadjuvant RT, both in univariate ($P < 0.05$) and multivariate analyses ($P < 0.05$). Determination of XPG C46T polymorphism could provide useful information to select patients who respond to common NCRT.

Local recurrence is a critical problem in rectal cancer. It is difficult to cure and is associated with a poor prognosis. It also has a profound negative effect on quality of life because it involves severe suffering for the patient, with pain, bleeding, ulceration, and fistulation as common associated symptoms [25]. In our serial of patients, Forty-six of them died of the disease recurrence and metastasis, and Cox proportional hazard model showed that CT stage, CN stage and XPG C46T genotype were both found to be independent predictors of outcome. The CT stage and CN stage have previously been identified as a strong prognostic indicator [26, 27].

In summary, our results supported the hypothesis that tagSNPs in the XPG C46T (rs1047768) may contribute toward rectal cancer patients' response to platinum agents. The determination of genetic profiles may assist in the selection patients who are likely to benefit from a specific chemoradiotherapy, since chemoradiotherapy regimens tailored to individual patients may help to improve response and quality of life.

The limitation in our study is that it is a retrospective study, and the sample size was not large, which may decrease the statistical power of our study and thus lower the power to find the differences between groups. Additionally, some uncontrolled or unmeasured factors, such as experimental error, may potentially produce bias. Therefore, Additional well-designed, large sample, multicenter, prospective studies are needed to confirm the result of our study.

In conclusion, our study found that XPG C46T C/C is associated with response to XELOXART Trial and prognosis in clinical stage II/III rectal cancer received XELOXART Trial. Additional well-designed, large sample, multicenter, prospective studies are needed to confirm the result of this study.

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Disclosure ofconflict of interest

None.

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