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RAPID COMMUNICATION

ERCC1 polymorphism, expression and clinical outcome of oxaliplatin-based adjuvant chemotherapy in gastric cancer

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Abstract

AIM: To determine the influence of excision repair cross complementing group 1 (*ERCC1*) codon 118 polymorphism and mRNA level on the clinical outcome of gastric cancer patients treated with oxaliplatin-based adjuvant chemotherapy.

METHODS: Eighty-nine gastric cancer patients treated with oxalipatin-based adjuvant chemotherapy were included in this study. *ERCC1* codon 118 C/T polymorphism was tested by polymerase chain reaction-ligation detection reaction (PCR-LDR) method in peripheral blood lymphocytes of those patients; and the intratumoral *ERCC1* mRNA expression was measured using reverse transcription PCR in 62 patients whose tumor tissue specimens were available.

RESULTS: No significant relationship was found between *ERCC1* codon 118 polymorphism and *ERCC1* mRNA level. The median relapse-free and overall survival period was 20.1 mo and 28.4 mo, respectively. The relapse-free and overall survivals in patients with low levels of *ERCC1* mRNA were significantly longer than those in patients with high levels ($P < 0.05$), while there was no significant association found between *ERCC1* 118 genotypes and the disease prognosis. Multivariate analysis also showed that *ERCC1* mRNA level was a potential predictor for relapse and survival in gastric cancer patients treated with oxaliplatin-based adjuvant chemotherapy ($P < 0.05$).

CONCLUSION: *ERCC1* codon 118 polymorphism has no significant impact on *ERCC1* mRNA expression, and the intratumoral *ERCC1* mRNA level but not codon 118 polymorphism may be a useful predictive parameter for the relapse and survival of gastric cancer patients receiving oxaliplatin-based adjuvant chemotherapy.

Key words: Gastric cancer; Adjuvant chemotherapy; Excision repair cross complementing group 1; Gene polymorphism

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INTRODUCTION

In China, gastric cancer is the leading cause of cancer deaths, accounting for nearly one-fourth of all cancer deaths. Surgery is the primary modality for managing early-stage and locally-advanced disease. However, even after gastrectomy, the majority of patients develop local or distant recurrence[1]. Adjuvant chemotherapy for gastric cancer has been under clinical investigation for more than four decades. Fluoropyrimidines, platinum-drugs and taxanes were shown to be effective in the treatment of gastric cancer. However, the response rates of these drugs or their combinations were less than 50%[2,3]. There is no standard regimen for postoperative treatment at the moment. Having an effective assay to predict the response to a given chemotherapeutic protocol beforehand would greatly enhance the success rate as well as the life quality of the patients.

The nucleotide excision repair (NER) system plays a significant role in repairing a variety of distorting

lesions, including platinum-drug induced DNA adducts. Oxaliplatin is a platinum-based therapeutic agent that has shown anti-tumor activities in gastric cancer. Resistance to oxaliplatin has been attributed to enhanced tolerance and repair of DNA damage through the NER pathway. As an excision nuclease within the NER pathway, excision repair cross complementing group 1 (*ERCC1*) has been reported to play a major role in the response to platinum-based chemotherapy. Studies have shown that the higher the *ERCC1* expression levels, the less sensitive the tumors to platinum therapies[4-7]. Recently, a single nucleotide polymorphism at codon 118 (C→T) was reported to be associated with altered *ERCC1* mRNA levels[8] and clinical outcome in cancer patients treated with platinum-based chemotherapy[9-12]. However, the results about the relationship among *ERCC1* codon 118 polymorphism, *ERCC1* mRNA level and platinum sensitivity are controversial. In this study, we investigated whether the *ERCC1* codon 118 polymorphism could influence *ERCC1* mRNA expression, and whether the polymorphism, and the intratumoral *ERCC1* mRNA expression have the prognostic value for the gastric cancer patients receiving oxaliplatin-based adjuvant treatment.

MATERIALS AND METHODS

Patients

From June 2001 to March 2006, 89 patients with histologically confirmed gastric cancer were enrolled in this study at the 4th Affiliated Hospital of Suzhou University. Inclusion criteria included: (1) patients without early recurrence or incurable resection, (2) patients receiving no other adjuvant treatment, such as radiotherapy or immunotherapy, and (3) patients with their performance status score of 0-1 and a life expectancy over 6 mo. All those patients received radical surgery, and then were treated with at least four cycles of oxaliplatin-based adjuvant treatment, including 70 with 5-FU/leucovorin/oxaliplatin (FOLFOX4: oxaliplatin 85 mg/m^2 and leucovorin 400 mg/m^2 followed on days 1 and 2 by 5-FU 400 mg/m^2 intravenous (IV) bolus, then 600 mg/m^2 IV over 22-h continuous infusion, and repeated every 2 wk), 9 with 5-FU/leucovorin/oxaliplatin/other regimens (taxanes or hydroxycamptothecin) (paclitaxel 135 mg/m^2 or docetaxol 75 mg/m^2 on day 1, hydroxycamptothecin 8 mg/m^2 on days 1-5; and the usage of 5-FU and leucovorin was the same as that in FOLFOX4). If patients had hematologic toxic effects of -grade 3 or grade 4 or nonhematologic toxic effects of grades 2-4, their daily dose was reduced properly.

Blood samples were collected in EDTA-containing tubes from gastric cancer patients before surgery or chemotherapy, and tumor tissue samples were obtained during surgery, and stored in liquid nitrogen until preparation of RNA extracts. Follow-up of those patients was made at 3-mo intervals after chemotherapy at outpatient clinics or by routine phone calls. This study was approved by the ethics and research committee of our hospital.

Table 1 The sequences of primers and probes

Primers or probes	Sequences (5'-3')	Length of product (bp)
actin-U	AGAAGATGACCCAGATCATGTT	290
actin-L	CTTAATGTCACGCACGATTTCC	
ERCC1-U	TACCACAACCTGCACCCAGACTAC	321
ERCC1-L	CTGACTGTCCGTTTTGTTGACTGA	
ERCC1-118-U	GGTCATCCCTATTGATGGCTTCTG	154
ERCC1-118-L	AGCTCACCTGAGGAACAGGGCACAG	
ERCC1-118-P	p-TTGCGCACGAACTTCAGTACGGGAT GGGACACTAATCGGAGGATTA-FAM	
ERCC1-118-T	CTACGGAG GATTATGAGGAGCTGCGT CGCCAAATTCCCAGGGCACA	92
ERCC1-118-C	CTACGAAATCAGGAGGATTATGAGGA GACGTCGCCAAATTCCCAGGG CACG	97

Genotyping of ERCC1 codon 118 polymorphism

Genomic DNA was isolated from peripheral blood lymphocytes using Axygene genomic DNA purification kit (Axygen Biotechnology, China). The primers and probes are listed in Table 1. Genotyping of *ERCC1* codon 118 was performed using polymerase chain reaction-ligation detection reaction (PCR-LDR) method as described previously[13].

Relative quantitative analysis of ERCC1 mRNA using reverse transcription-polymerase chain reaction (RT-PCR)

Total RNA was extracted from 62 tumor tissues using Trizol (Invitrogen Corporation, CA) according to the manufacturer's instructions. The amount of total RNA was estimated by ultraviolet absorbance at 260 nm, and the quality was determined by agarose gel electrophoresis in the presence of formaldehyde. cDNA strand synthesis was performed using a reverse transcription system (Promega Corporation, US).

ERCC1 and an internal reference gene (β-*actin*) cDNA fragments were amplified separately by PCR in triplicates. The PCRs were carried out in a total volume of 25 μL including 2 μL cDNA, 1× PCR buffer, 1.5 mmol/L $MgCl_2$, 0.2 mmol/L dNTPs, 0.5 μmol/L each primer, 1 U hot-start Taq DNA polymerase (QIAgen). Cycling parameters were as follows: 95℃ for 15 min; 35 cycles of 94℃ for 40 s, 52℃ for 30 s, and 72℃ for 30 s; and a final extension step at 72℃ for 10 min. PCR products were analyzed by 2% agarose gel electrophoresis, and ethidium bromide staining following by visualization with ultraviolet illumination using a gel imaging analyzing system. *ERCC1* amplification products were calculated as a ratio of the gray scale of *ERCC1* to that of β-*actin*.

Statistical analysis

Data analysis was performed using SPSS 13.0 for Windows. *ERCC1* levels were categorized into a low and high value using the median concentration as a cut-off point. The relationship between the genotype frequencies, mRNA, levels and clinical characteristics were assessed by χ^2 or Fisher's exact probability tests. The Mann-Whitney *U* test was used to assess the correlation between *ERCC1* genotypes and mRNA levels. Relapse-free survival (RFS) was defined as the

Table 2 Relationship among *ERCC1* genotypes, mRNA expression and clinical characteristics of gastric cancer

Clinical characteristics	*n*	*ERCC1* polymorphism		χ^2	*P*	*ERCC1* mRNA		χ^2	*P*
		C/C (*n* = 45)	C/T + T/T (*n* = 44)			High value (*n* = 31)	Low value (*n* = 31)		
Age (yr)									
⩾ 58	48	25	23	0.096	0.833	18	18	0	1.000
< 58	41	20	21			13	13		
Gender									
Male	66	31	35	1.318	0.334	20	24	0.253	0.402
Female	23	14	9			11	7		
TNM stage									
I - II	19	13	6	3.082	0.079	6	6	0	1.000
III-IV	70	31	39			25	25		
Grading									
G2	45	20	24	0.552	0.527	15	19	1.042	0.444
G3	44	21	20			16	12		

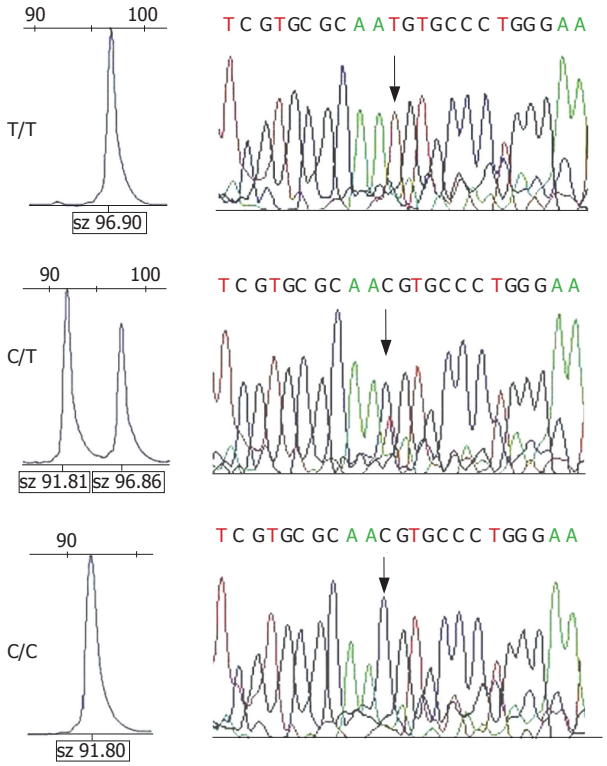

Figure 1 Genotyping results of *ERCC1* codon 118 polymorphism electrophoresis results of PCR-LDR products with different genotypes and its sequencing results. LDR products of *ERCC1* 118 C/C and T/T were 92 and 97 base pairs. The SNP sites are indicated by the arrowhead. The results were completely matched to the corresponding results derived from PCR-LDR.

time interval between the date of surgery and the date of confirmed relapse or the date of last follow-up. Overall survival (OS) was defined as the time between surgery and death. Survival curves were generated by the Kaplan-Meier method, and verified by the log-rank test. Cox proportional hazards regression analysis was used to estimate odds ratios (ORs) and their 95% confidence intervals (CIs), representing the overall relative risk of relapse and death associated with *ERCC1* polymorphism or expression, and to adjust for potential confounding variables. All of the values were two-sided and statistical significance was defined as $P < 0.05$.

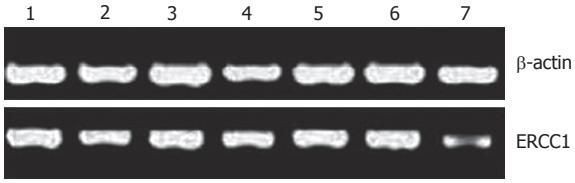

Figure 2 RT-PCR results of *ERCC1* mRNA in gastric cancer tissues.

RESULTS

ERCC1 genotypes and mRNA expression

A total of 89 patients were analyzed. Their demographic and disease characteristics are shown in Table 2. The allelic discrimination data from PCR-LDR assay were confirmed by direct sequencing of representative PCR products (Figure 1). Of the 89 patients, the frequencies of *ERCC1* codon 118 C/C, C/T and T/T were 50.6% (45/89), 42.7% (38/89) and 6.7% (6/89); and the allele frequencies of A and T were 71.9% and 28.1%, respectively. Genotype distribution of *ERCC1* codon 118 was consistent with the Hardy-Weinberg equilibrium among patients ($\chi^2 = 0.288$, $P > 0.05$).

Gastric cancer tissue samples were available in 62 patients. The intratumoral expression of *ERCC1* mRNA in those tissues was tested by semi-quantitative RT-PCR (Figure 2). A marked inter-individual variation in *ERCC1* mRNA expression in the 62 samples was observed: *ERCC1*/β-*actin* ratios ranged from 0.087 to 1.006 with a median value of 0.672. The median value was assigned as the cut-off value to divide those 62 patients into two groups with high or low *ERCC1* mRNA values.

No significant relationship was found between *ERCC1* expression and *ERCC1* codon 118 genotypes (the median *ERCC1* expression was 0.680 for C/C and 0.665 for C/T + T/T; $Z = -0.592$, $P = 0.554$) (Figure 3).

No significant association was found between age, gender, stage or grading and *ERCC1* codon 118 polymorphism or mRNA levels, except that a trend was found between the polymorphism and stage ($P = 0.079$) (Table 2).

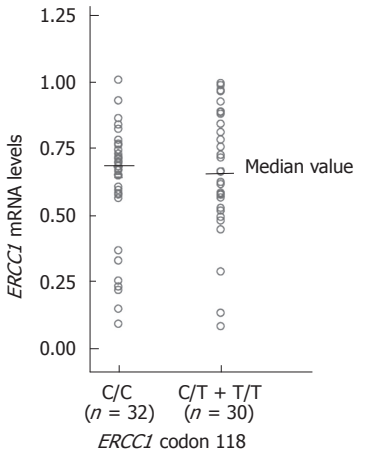

Figure 3 Relationship between *ERCC1* mRNA levels and codon 118 polymorphism.

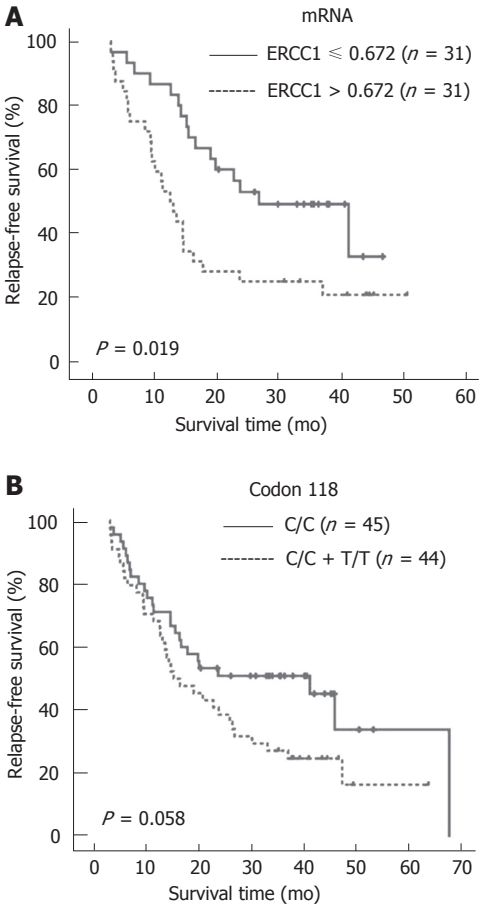

Figure 4 Relapse-free survival curves of gastric cancer patients according to *ERCC1* mRNA expression and *ERCC1* 118 C/T polymorphism relapse-free survival curves according to *ERCC1* mRNA expression (A) or *ERCC1* 118 polymorphism (B). The relapse-free survival in patients with high levels of *ERCC1* mRNA (> 0.672) was significantly poorer than that in patients with low levels (⩽ 0.672) ($P < 0.05$), while there was no significant difference between patients with *ERCC1* 118 C/C and variant genotypes (T/T or C/T).

Associations between ERCC1 polymorphism, mRNA levels and clinical outcome

Patients with the C/C genotype showed a trend towards correlation with prolonged RFS when compared to those with the C/T + T/T genotypes (22.0 mo *vs* 16.5 mo, χ^2 = 3.602, $P = 0.058$, Figure 4A). The median OS was 29.8 (95% CI = 20.9-83.1) mo for the patients with the C/C genotype, and 26.4 (95% CI = 22.1-34.7) mo in those with the C/T or T/T genotype ($\chi^2 = 1.548$, $P = 0.214$) (Figure 5A). The median RFS was 23.8 mo in patients with low *ERCC1* values, but only 13.2 mo in patients with high *ERCC1* levels ($\chi^2 = 5.464$, $P = 0.019$) (Figure 4B). A significant difference in OS also was found between the groups with low *ERCC1* levels and high *ERCC1* levels (29.6 mo *vs* 18.7 mo, $\chi^2 = 4.546$, $P = 0.033$) (Figure 5B).

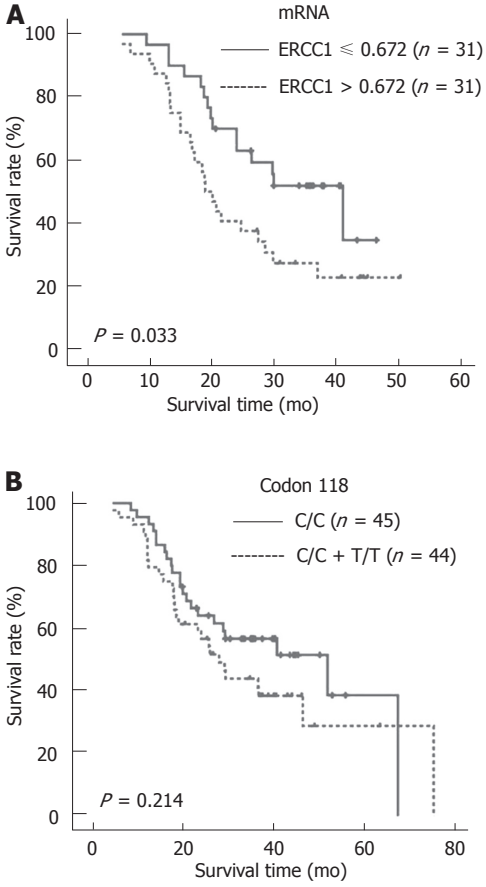

Figure 5 Overall survival curves of gastric cancer patients according to *ERCC1* mRNA expression and *ERCC1* 118 C/T polymorphism survival curves according to *ERCC1* mRNA levels (A) or *ERCC1* 118 polymorphism (B). The overall survival in patients with low level of *ERCC1* mRNA was significantly longer than that in patients with high levels ($P < 0.05$), while there was no significant difference found between patients with *ERCC1* 118 C/C and variant genotypes (T/T or C/T).

Cox multivariate analysis showed that, after adjustment for age, gender, stage and grading, a high *ERCC1* mRNA level appeared to be an independent risk factor for RFS (adjusted OR = 2.493, 95% CI: 1.291-4.814, $P = 0.006$) and OS (adjusted OR = 2.449, 95% CI: 1.264-4.743, $P = 0.008$). No significant association was found between *ERCC1* codon 118 genotypes and RFS (adjusted OR = 1.644, 95% CI = 0.954-2.833, $P = 0.074$) or OS (adjusted OR = 1.310, 95% CI = 0.727-2.358, $P = 0.369$).

DISCUSSION

Optimal chemotherapeutic treatment would allow clinicians to maximize the benefits of cancer

chemotherapy. Successful adjuvant chemotherapy following gastrectomy is crucial for a favorable outcome in gastric cancer. However, few prognostic and predictive markers have been identified to individualize treatment, maximize therapeutic effect. The *ERCC1* expression and codon 118 polymorphism have been reported to influence platinum-based drug sensitivity in advanced or metastatic cancers. The aim of this study was to determine whether *ERCC1* codon 118 polymorphism could influence the intratumoral *ERCC1* mRNA level and predict the clinical outcome of gastric cancer patients treated with oxaliplatin-based adjuvant chemotherapy.

Some studies suggested that impaired DNA repair within the tumor could lead to the decreased removal of platinum-DNA adducts and, therefore, increased clinical response to platinum chemotherapy. *ERCC1* mRNA level has been shown to correlate with nucleotide excision repair capacity. Chinese hamster ovary cells, which do not express a functional ERCC1 protein, are more susceptible to platinum-drugs than the parental cell line with normal ERCC1[4]. So it is naturally expected that the higher the levels of *ERCC1* expression, the less susceptible the tumors to platinum agents. Recently, a synonymous polymorphism at codon 118 converting a common codon usage (AAC) to an infrequent one (AAT), both coding for asparagine, has been associated with reduced mRNA and protein levels[8]. However, the assumed relationship between *ERCC1* codon 118 polymorphism and expression was not always observed[14]. In this study, the *ERCC1* mRNA levels in patients with C/C genotype was higher than that in patients with C/T or T/T genotype; but the difference failed to reach statistical significance ($P > 0.05$), which suggested that the polymorphism may have limited impact on *ERCC1* mRNA levels. In addition, the possibility that *ERCC1* codon 118 polymorphism is in linkage disequilibrium with other *ERCC1* mutations or polymorphisms that directly affect its expression also cannot be ruled out. Other possible reasons may be the relatively small sample size of the present study, and the quantitative method for *ERCC1* mRNA expression used in this study. In the future, using more accurate real-time quantitative RT-PCR assay on the large number of patients may help us to give more persuasive data on the putative association.

Although *ERCC1* codon 118 polymorphism has been extensively studied for its involvement in carcinogenesis[15,16], the predictive value of the polymorphism on platinum chemotherapy has not been studied thoroughly. The functional importance of this polymorphism is still under debate. A limited number of studies suggest that the favorable prognosis seems associated with the T allele[12,17-19]; but controversial results also exist[9-11,20,21]. Viguier *et al*[12] and Martinez-Balibrea *et al*[19] found that colorectal cancer patients with the *ERCC1* 118 T/T genotype were more likely to respond to oxaliplatin-based chemotherapy than carriers of the other genotypes. The favorable effect of T/T genotype also was found in lung cancer[22], pancreatic cancer[23], and ovarian cancer[18] patients treated with platinum-based chemotherapy. However, other studies on lung cancer[10] and colorectal cancer[9,11,20,21] showed opposite results. In addition, several studies demonstrated that no clear association was found between *ERCC1* codon 118 polymorphism and platinum sensitivity[24-26]. In a recent study on advanced gastric cancer treated with fluorouracil/cisplatin palliative chemotherapy, a tendency to higher response rate was found in patients with C allele ($P = 0.09$). In this study, patients with the C/C genotype also showed a trend to prolonged RFS when compared to those with the other genotypes, while no significant relationship was found between *ERCC1* codon 118 genotypes and OS. The small sample size ($n = 89$) of the present study might remain a limitation to clarify the exact role of *ERCC1* codon 118 polymorphism. Other possible reasons for controversial results may include genotyping in normal or tumor tissues, variable doses and schedules of platinum-based therapy, different ethnic populations, variable tumor stage and different kind of cancers.

A limitation of the presented study is that we only analyzed germline genotype. The germline genotypes offer better clinical accessibility and applicability, compared to tumor tissue, which presents difficulties in obtaining and handling samples. To analyze somatic genotype from tumor tissues was not easy. It is difficult to purify malignant cells from miscellaneous normal cells in clinical tumor tissue even using laser microdissection. The classification of a certain gene polymorphism may be hampered in a mixture of normal and malignant cells, which has been clearly illustrated by loss of heterozygosity. The correlation between germline genotype from peripheral blood and tumor tissue should be considered. To the best of our knowledge, there are no related reports on the impact of LOH on *ERCC1* polymorphism in gastric cancer. Hence, the possible influence of LOH on *ERCC1* genotyping should be discussed in the future.

Relative consensus conclusions were obtained regarding the effect of *ERCC1* expression on platinum-drug sensitivity. A multi-centers study on non–small-cell lung cancer found that cisplatin-based adjuvant chemotherapy significantly prolonged survival among patients with ERCC1-negative tumors, but not among patients with ERCC1-positive tumors[5]. In advanced gastric cancer patients treated with 5-FU and oxaliplatin, favorable response rate and survival were also found in patients without ERCC1 protein expression[7]. Other studies showed that the low intratumoral *ERCC1* mRNA expression was associated with favorable clinical outcomes after treatment with platinum-based chemotherapy in lung cancer[27,28], colorectal cancer[29], gastric cancer[30-32], ovarian cancer[33], bladder cancer[34], head and neck cancer[35]. A recent phase Ⅲ trial in non-small-cell lung cancer also demonstrated that assessment of intratumoral *ERCC1* mRNA expression is feasible in the clinical setting and predicts response to cisplatin[36]. However, most of those studies focused on the influence of *ERCC1* expression on the effect of platinum-drug in advanced or metastatic diseases, little was known about its effect on platinum-drug adjuvant chemotherapy. Our

results suggested that low *ERCC1* mRNA level appeared to be an independent prognostic factor for better prognosis, which is consistent with the results observed in advanced gastric cancer[30-32].

In conclusion, *ERCC1* codon 118 polymorphism has no significant effect on *ERCC1* mRNA expression; and the intratumoral *ERCC1* mRNA level, but not *ERCC1* codon 118 polymorphism may be an important prognostic marker for the clinical outcome of gastric cancer patients treated with oxaliplatin-based adjuvant chemotherapy. Detection of the intratumoral *ERCC1* mRNA expression may give meaningful clinical information with respect to the rational choice platinum compound in the treatment of gastric cancer.

COMMENTS

Background

Oxaliplatin is one of the most effective agents against gastric cancer; its efficacy rate differs greatly among patients. Resistance to oxaliplatin has been attributed to enhanced tolerance and repair of DNA damage. Excision repair cross complementing group 1 (ERCC1) has been reported to play a major role in the response to platinum chemotherapy, but little is know about the effect of *ERCC1* codon 118 polymorphism and expression on clinical outcome of oxaliplatin-based adjuvant chemotherapy in gastric cancer.

Research frontiers

ERCC1 has been reported to play a major role in the response to platinum chemotherapy. Studies have shown that the higher the *ERCC1* expression levels, the less sensitive the tumors to platinum therapies. Recently, a single nucleotide polymorphism at codon 118 (C→T) was reported to be associated with altered *ERCC1* mRNA levels and clinical outcome in cancer patients treated with platinum-based chemotherapy. However, the results about the relationship among *ERCC1* codon 118 polymorphism, *ERCC1* mRNA level and platinum sensitivity are controversial.

Innovations and breakthroughs

No significant relationship was found between *ERCC1* codon 118 polymorphism and *ERCC1* mRNA levels. It is found that *ERCC1* mRNA level but not codon 118 polymorphism was a potential indicator in predicting the relapse and survival of gastric cancer patients treated with oxaliplatin-based adjuvant chemotherapy. To our knowledge, it is the first report to study the effect of intratumoral *ERCC1* expression and *ERCC1* codon 118 polymorphism on clinical outcome of oxaliplatin-based adjuvant chemotherapy in Chinese patients with gastric cancer.

Applications

Controlled, prospective clinical trials are required to confirm our results and to establish the advantage of pre-treatment tumor biopsy for *ERCC1* screening, which permits a more rational decision on whether to precede an oxaliplatin-based adjuvant chemotherapy. So patients who are unlikely to respond may spare unnecessary toxicity and can be treated with alternative drugs.

Terminology

Oxaliplatin is a widely applied medicine for chemotherapy of gastrointestinal cancer. ERCC1 is an important enzyme for DNA repair.

Peer review

This is a good study. Over all the study has clinical relevance for LDLT programmes.

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