Expression of ERCC1 and TYMS in colorectal cancer patients and the predictive value of chemotherapy efficacy

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Abstract. The present study investigated the expression of excision repair cross-complementing gene 1 (ERCC1) and thymidylate synthase (TYMS) in patients with colorectal cancer and the predictive value of chemotherapy. Eighty patients with colorectal cancer chemotherapy admitted to Binzhou Medical University Hospital from June 2013 to June 2015 were randomly selected, and 80 cancer tissues and 68 adjacent tissues were taken for analysis. RT-qPCR was used to detect ERCC1 as well as the expression level of TYMS. The relationship of the expression level with the chemotherapy efficacy, clinical pathology and survival time in colorectal cancer patients receiving standard chemotherapy, was compared. The expression of ERCC1 and TYMS mRNA in cancer tissues was significantly higher than that in the adjacent tissues (P<0.05). There was no correlation between ERCC1 mRNA expression, TYMS mRNA and clinicopathological features of colorectal cancer (P>0.05). The predictive effect of ERCC1 on colorectal cancer chemotherapy was 0.919 (95% CI, 0.862-0.976), P<0.001. The AUC of TYMS for predicting the efficacy of chemotherapy on colon cancer was 0.831 (95% CI, 0.735-0.926), and both had higher predictive values. The expression levels of ERCC1 and TYMS mRNA in 80 patients with colorectal cancer were divided into the low and high expression groups. The 3-year survival rate of patients in the low expression group was significantly higher than that in the high expression group, and the difference between the two groups was statistically significant (P<0.05). ERCC1 and TYMS had a high predictive value for the efficacy of chemotherapy in patients with colorectal cancer, and patients with lower expression of ERCC1 and TYMS had improved 3-year survival rates than patients with higher expression. Therefore, for patients with colorectal cancer, ERCC1 and TYMS can be used as predictors of the efficacy of chemotherapy.

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Introduction

Colorectal cancer is a common malignant tumor of the digestive tract, due to its insidious early onset, it is often in the advanced-stage at the time of diagnosis, which is a major threat to human health (1). Currently, the main treatment of colorectal cancer is still a comprehensive treatment based on surgery. However, there is a huge difference in the treatment effect of the same regime in different patients (2). At present, the basic drug for colorectal cancer chemotherapy is still 5-fluorouracil (5-FU), also FOFOX treatment with 5-FU as the main drug (oxaliplatin combined with 5-FU and calcium leucovorin) can prolong the survival time of patients with colorectal cancer (3). However, since the current FOLFOX regimen is not effective for all patients with advanced colorectal cancer, the method to predict the efficacy of chemotherapy and adjust the treatment plan according to the patient's specific situation is a problem that needs to be solved clinically (4).

DNA excision repair cross-complementing gene 1 (ERCC1) is a gene closely related to tumor resistance and DNA repair (5). Studies have shown that elevated ERCC1 gene expression suggests that patients have a poor sensitivity to platinum-based chemotherapy drugs (6). Thymidylate synthetase (TYMS) is also a common drug resistance factor in colon cancer (7). TYMS acts as a rate-limiting enzyme for the synthesis of pyrimidine nucleotides, it is also a target enzyme that 5-FU can exert cytotoxicity, studies have reported that patients with lower levels of TYMS are more sensitive to 5-FU (8-10). However, there are studies showing that TYMS is not significantly correlated with patient sensitivity to 5-FU (11).

Therefore, we explored the relationship of ERCC1 and TYMS expression in colorectal cancer patients after chemotherapy and their chemotherapy efficacy. This is expected to provide a theoretical basis for individual optimization of clinical chemotherapy regimens.

Patients and methods

General information. Eighty patients with colorectal cancer admitted to Binzhou Medical University Hospital (Binzhou, China) from June 2013 to June 2015 were randomly selected,

Table I. Primer sequences.

Gene names	Upstream primer	Downstream primer
ERCC1	5'-CTCAAGGAGCTGGCTAAGATGT-3'	5'-CATAGGCCTTGTAGGTCTCCAG-3'
TYMS	5'-CCTGAATCACATCGAGCCACTG-3'	5'-GCACCCTAAACAGCCATTTCCA-3'
GAPDH	5'-TCATGGGTGTGAACCATGAGAA-3'	5'-GGCATGGACTGTGGTCATGAG-3'

and 80 cancer tissues and 68 adjacent tissues were taken for analysis, including 48 male and 32 female patients, and the mean age was 52.5±9.6 years. Among them, the pathological differentiation was divided into 23 patients with high differentiation, 35 patients with moderate differentiation and 22 patients with low differentiation, the average distance of the tumor from the anal margin was 4.24±1.73 cm. Inclusion criteria were: Patients diagnosed with colorectal cancer by pathological diagnosis; patients with a predicted survival time of >3 months. Exclusion criteria were: Patients without adequate pathology for testing, patients with symptomatic or uncontrollable brain metastases; patients with metabolic disorders with fluorouracil or with platinum chemotherapeutic drugs; patients with severe liver and kidney dysfunction; patients with cognitive or communication impairments; patients with poor compliance. All the patients and their families agreed to participate in the experiment and signed the informed consent form. This study was approved by the Binzhou Medical University Hospital Ethics Committee.

Experimental drugs and reagents. Oxali Platinum was purchased from Zhengda Tianqing Pharmaceutical Group Co., Ltd., the national medicine standard is H20143263. Calcium leucovorin was purchased from Jiangsu Hengrui Pharmaceutical Co., Ltd., the national medicine standard is H20080718. 5-FU was purchased from Tianjin Taihe Pharmaceutical Co., Ltd., the national medicine standard is H12020675, the real-time quantitative PCR instrument was purchased from Bio-Rad Laboratories, qPCR kit and miScript Reverse Transcription kit were purchased from Takara Biotechnology, Co., Ltd.

Chemotherapy regime. Oxaliplatin was intravenously instilled at a concentration of 110 mg/m^2 for 2 h on the 1st and 15th day, calcium leucovorin was intravenously infused at a concentration of 200 mg/m^2 for 2 h on the 1st and 15th day, 5-FU was continuously pumped for 22 h at concentrations of 2.4 g/m^2 on the 1st and 2nd day, and again on the 15th and 16th day at a concentration of 2.4 g/m^2. After 4 cycles, the patient's chemotherapy efficacy and toxic side effects were evaluated.

RT-qPCR detection of RNA. Colon cancer tissue and adjacent cancer tissue was removed from a liquid nitrogen tank. First, the tissue standard was made into paraffin section specimens, then the specimen was added to the centrifuge tube and 1 ml of tissue transparent solution was added to the centrifuge tube. After dewaxing, the tissue transparent solution was removed with absolute ethanol and then air drying was applied. Following air drying, the protease and lysate were added, then DNase was added and centrifuged at 4,000 x g for 10 min at 4˚C to obtain RNA. Next, 5 μg of total RNA was taken for reverse transcription of cDNA according to the kit instructions. The reaction parameters were: 37˚C for 45 min, 95˚C for 5 min. SYBR-Green PCR amplification (Thermo Fisher Scientific, Inc.) was applied to the post-transcribed cDNA, with GAPDH as an internal reference. The primer sequences are shown in Table I. PCR reaction conditions were: 94˚C for 10 min, 95˚C for 30 sec, 60˚C for 45 sec, for 40 cycles. RT-PCR was performed using a PCR instrument, and the experiment was repeated 3 times. The result were quantified with $2^{-\Delta\Delta Cq}$ method (12).

Table II. Comparison of expression of ERCC1 and TYMS mRNA in colorectal cancer tissues and adjacent tissues.

Gene name	Cancer tissues (n=80)	Adjacent tissues (n=68)	t	P-value
ERCC1	1.09±0.11	0.39±0.14	34.04	<0.001
TYMS	1.03±0.12	0.38±0.11	34.11	<0.001

Observation indices. i) Expression of ERCC1 and TYMS mRNA in colorectal cancer tissues and adjacent tissues. ii) According to the average number of ERCC1 mRNA and TYMS mRNA in patient cancer tissues. The patients with colorectal cancer were divided into ERCC1 and TYMS high expression group and the low expression group, then the relationship between the expression of ERCC1 and TYMS and the clinicopathological characteristics was analyzed. iii) The efficacy of chemotherapy in patients with colorectal cancer was evaluated and divided into complete remission, partial remission, stabilization, and progression based on chemotherapy efficacy. Number of complete remissions + number of partial remissions = number of effective chemotherapy, number of patients with no progression + number of patients with progression = number of non-effective chemotherapy, and the predictive value of ERCC1 and TYMS expression in the cancerous tissues was evaluated. iv) The relationship between ERCC1 and TYMS expression and 3-year survival rate in patient with colorectal cancer was analyzed.

Statistical analysis. This study used SPSS 15.0 software package (SPSS Inc., Chicago, IL, USA) to perform statistical analysis on experimental data. Countable data were obtained by Chi-square test, and measurement data were expressed using mean ± standard deviation (SD). The t-test was used for comparison between the groups, the experimental graph was plotted by GraphPad Prism 6 software (GraphPad Software, Inc.). Survival

Table III. Relationship between the expression of ERCC1 and TYMS mRNA and the clinicopathological features in cancer tissues [n, (%)].

Factors	ERCC1X2				TYMS			
	High expression (n=29)	Low expression (n=51)	χ^2	P-value	High expression (n=31)	Low expression (n=49)	χ^2	P-value
Sex			0.036	0.849			0.079	0.779
Male	17 (58.62)	31 (60.78)			18 (58.06)	30 (61.22)		
Female	12 (42.38)	20 (39.22)			13 (41.94)	19 (38.78)		
Age (years)			0.004	0.949			0.003	0.959
>52	14 (48.28)	25 (49.02)			15 (48.39)	24 (48.98)		
≤52	15 (51.72)	26 (50.98)			16 (51.61)	25 (51.02)		
Degree of differentiation			0.287	0.867			0.116	0.944
High	8 (27.59)	15 (29.41)			9 (29.03)	14 (30.61)		
Moderate	12 (41.38)	23 (45.10)			13 (41.94)	22 (44.90)		
Low	9 (31.03)	13 (25.49)			9 (29.03)	13 (24.49)		
Tumor types			0.011	0.994				
Ulcer type	10 (34.48)	18 (35.29)			10 (32.26)	18 (32.65)		
Lump type	9 (31.03)	16 (31.37)			10 (32.26)	15 (34.69)		
Infiltrating	10 (34.48)	17 (58.62)			11 (35.48)	16 (32.65)		
Tumor location			0.000	0.986				
Left colon	12 (41.38)	21 (41.18)			13 (45.16)	20 (46.94)		
Right colon	17 (58.62)	30 (58.82)			18 (54.84)	29 (53.06)		

Table IV. Comparative gene expression of ERCC1 and TYMS mRNA in patients with different chemotherapy efficacy.

Items	Effective group (n=56)	Non-effective group (n=24)	t	P-value
ERCC1	1.08±0.13	0.89±0.11	6.258	<0.001
TYMS	1.09±0.10	0.91±0.13	6.725	<0.001

analysis was performed using Kaplan-Meier and log-rank test. ROC curve was used for chemotherapy efficacy analysis. The efficacy was shown as 95% CI (Confidence Interval). P<0.05 was considered as a statistically significant difference.

Results

Expression of ERCC1 and TYMS mRNA in colorectal cancer tissues and adjacent tissues. The expression of ERCC1 mRNA in cancer tissues was significantly higher than that in adjacent tissues, and the difference was statistically significant (P<0.05). The expression of TYMS mRNA in cancer tissues was significantly higher than that in adjacent tissues, and the difference was statistically significant (P<0.05) (Table II).

Relationship between the expression of ERCC1 mRNA and TYMS mRNA and the clinicopathological features in cancer tissues. The expression of ERCC1 mRNA ≤1.09 was set as the low expression group (n=51), >1.09 was set as the high expression group (n=29). The expression of TYMS mRNA ≤1.03 was set as the low expression group (n=49), and >1.03 was set as the high expression group (n=31). Then the relationship between the expression of ERCC1 mRNA and TYMS mRNA and clinicopathological features was analyzed. There was no significant relationship between the expression of ERCC1 mRNA and TYMS mRNA in cancer tissues in terms of sex, age, degree of differentiation, tumor type and tumor location (P>0.05) (Table III).

Predictive value of ERCC1 mRNA and TYMS mRNA expression in cancer tissues for chemotherapy efficacy. After we evaluated the efficacy of chemotherapy in patients, the patients were divided into the chemotherapy-effective group (n=56) and the chemotherapy-ineffective group (n=24). The ERCC1 mRNA and TYMS mRNA expressions in the chemotherapy-effective group were 1.08±0.13 and 1.09±0.10, respectively. The expression of ERCC1 and TYMS mRNA in the chemotherapy-ineffective group was 0.89±0.11 and 0.91±0.13, respectively. The ROC curve showed that the AUC of ERCC1 for the prediction of chemotherapy efficacy in colon cancer was 0.919 (95% CI, 0.862-0.976), P<0.001. The AUC of TYMS for the prediction of chemotherapy efficacy in colon cancer was 0.831 (95% CI, 0.735-0.926), P<0.001 (Table IV and Figs. 1 and 2.

Survival analysis of ERCC1 mRNA and TYMS mRNA in both high and low expression groups. The 3-year survival rate of patients in the low expression group of ERCC1 was 60.78%

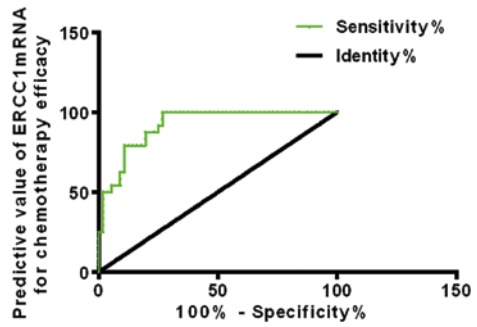

Figure 1. The predictive value of ERCC1 for chemotherapy efficacy. The AUC of ERCC1 mRNA expression for the prediction of chemotherapy efficacy was 0.919 (95% CI, 0.862-0.976), P<0.001.

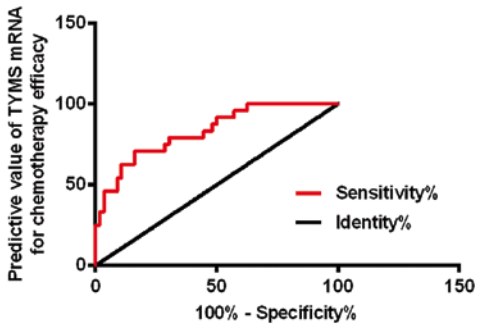

Figure 2. The predictive value of TYMS for chemotherapy efficacy. The AUC of TYMS mRNA expression for the prediction of chemotherapy efficacy was 0.831 (95% CI, 0.735-0.926), P<0.001.

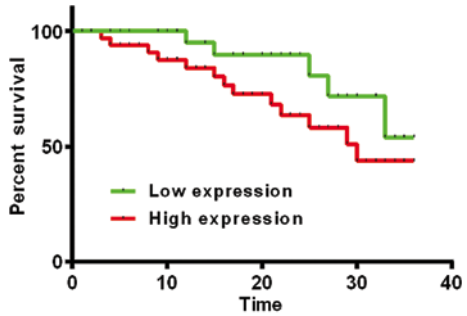

Figure 3. Effect of ERCC1 on patient 3-year survival rate. The 3-year survival rate of ERCC1 mRNA in the low expression group was significantly higher than that of the high expression group, and the difference was statistically significant (P<0.05).

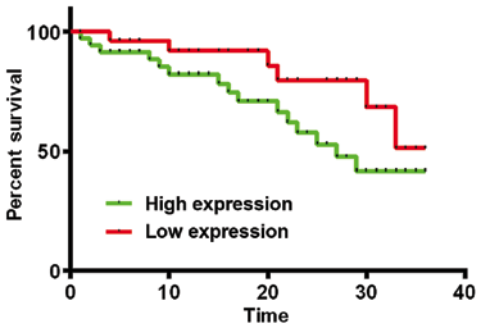

Figure 4. Effect of TYMS on patient 3-year survival rate. The 3-year survival rate of the patients with low expression of TYMS mRNA was significantly higher than that of the high expression group (P<0.05).

(31/51), the 3-year survival rate of patients in the high expression group was 41.38% (12/29). The 3-year survival rate of patients in the low expression group was significantly higher than that in the high expression group, and the difference was statistically significant (P<0.05). The 3-year survival rate of patients in the low expression group of TYMS was 61.22% (30/49), the 3-year survival rate of patients in the high expression group was 45.16% (14/31). The 3-year survival rate of patients in the low expression group was significantly higher than that in the high expression group of TYMS mRNA; the difference was statistically significant (P<0.05) (Figs. 3 and 4).

Discussion

In recent years, there have been many studies showing that the detection of certain genes can predict the sensitivity and efficacy of colorectal cancer chemotherapy drugs to some extent. This has a great significance for the optimization of treatments (13,14). Previous studies have reported that metastatic colon cancer has a 5-year survival rate of <40%. Even combined use of bevacizumab does not extend progression-free survival (15). There are also studies suggesting that one of the main factors affecting the prognosis of colon cancer is the efficacy of first-line chemotherapy (16). Therefore, the method of predicting the efficacy of first-line care for patients with clinical colon cancer is a clinically urgent problem. ERCC1, a very important gene in the DNA repair process, can form a heterodimer with the pigmented dry skin disease gene F. Heterodimers can cleave DNA single strands at the 5' end of the DNA damage site caused by platinum drugs, so this ensures the smooth repair of DNA (17). TYMS is an important rate-limiting enzyme that catalyzes the synthesis of pyrimidine nucleotides, studies have shown that its expression level may be related to the efficacy of chemotherapy with fluorouracils. The mechanism may be that fluorouracil forms a stable active metabolite by binding to TYMS. Therefore, the synthesis of TMP is inhibited, and finally the DNA strand is broken to affect the tumor cells of the patient (18,19).

In the present study, the expression of ERCC1 and TYMS mRNA in cancer tissues of patients with colorectal cancer after chemotherapy, and the relationship between its expression and the clinicopathological features, as well as the predictive value of chemotherapy efficacy and prognosis in patients were analyzed. The results showed that ERCC1 and TYMS mRNA were highly expressed in colorectal cancer patients. The patients were then divided into the high- and low-expression groups of ERCC1 and TYMS. The results showed that there was no significant association between ERCC1 and TYMS mRNA expression and clinical and pathological characteristics such as sex, age and pathological differentiation in colorectal cancer patients (P>0.05). Previous studies found that ERCC1 mRNA expression was negatively correlated with patient survival time and chemotherapy efficacy in the study on ERCC1 in postoperative non-small cell lung cancer (20). In our experiment, the results showed that the expression levels of ERCC1 mRNA and TYMS mRNA in the chemotherapy effective group were significantly lower than those in the chemotherapy non-effective group (P<0.05). The AUC of ERCC1 mRNA for the prediction of chemotherapy efficacy was 0.919. The AUC of TYMS mRNA

for the prediction of efficacy of chemotherapy is 0.830. The results suggest that the expression of ERCC1 mRNA and TYMS mRNA has a good predictive value for the chemotherapy efficacy of colorectal cancer. The 3-year survival rate of patients in the low expression group of both ERCC1 and TYMS was significantly higher than that of patients in the high expression group. The results suggest that patients in the low expression group of both ERCC1 mRNA and TYMS may benefit from first-line chemotherapy. Findings on the efficacy of chemotherapy in patients with gastric cancer have shown that patients with lower expression of ERCC1 mRNA have better efficacy for platinum-based chemotherapy (21), which is consistent with our conclusions. Regarding TYMS, some studies on prostate cancer patients found that the expression level of TYMS in patient cancer tissues was significantly higher than that in normal prostate tissues (22). In addition, it was found that the 1-year survival rate of non-small cell lung cancer patients with positive expression of *TYMS* gene was significantly lower than that of patients with negative expression (18). This is also consistent with our conclusions.

In summary, ERCC1 and TYMS are highly expressed in patients with colorectal cancer, and patients with lower expression of ERCC1 and TYMS mRNA are better than those with higher expression. The two genes have a high predictive value in efficacy, patients with lower ERCC1 mRNA and TYMS mRNA have a higher 3-year survival rate than patients with high expression. Therefore, for colorectal cancer patients, ERCC1 mRNA and TYMS mRNA can be used as predictors of the efficacy of chemotherapy. However, due to the sample size of the study, the patient's side effects and further molecular mechanisms were not explored. The efficacy predictions of the two factors for different chemotherapy regimes were also not compared. Future studies should focus on these aspects.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

HJ interpreted the data, designed and drafted the manuscript. HJ and BL performed PCR. FW and CM collected and analyzed the general data of the patients. TH assisted with the statistical analysis. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Binzhou Medical University Hospital (Binzhou, China). Patients who participated in this research had complete clinical data. Signed informed consents were obtained from the patients or the guardians.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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