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Original Article

Effects of DPYD and TS gene polymorphisms on chemosensitivity of 5-FU in advanced colorectal cancer

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Abstract: Dihydropyrimidine dehydrogenase (DPD) and thymidylate synthase (TS) play important roles in the process of cellular nucleic acid metabolism. The current study investigated the impact of DPYD and TS gene polymorphisms on 5-FU chemotherapy sensitivity of advanced colorectal cancer, aiming to provide a basis for individualized treatment of colorectal cancer (CRC) patients. One hundred patients with advanced CRC were enrolled. All patients were treated with fluorouracil-based systemic chemotherapy. Therapeutic effects and side effects of chemotherapy were evaluated. Polymorphisms of DPYD*5 and DPYD*9A, TS gene 5'-UTR, and 3'-UTR in the peripheral blood were detected. The impact of gene polymorphisms on chemotherapy and toxic side effects was analyzed. After chemotherapy, 10 patients achieved complete remission (CR), 33 patients achieved partial remission (PR), 28 patients showed stable disease (SD), and 29 patients showed disease progression (PD). Thus, the chemotherapy response rate was 43.00%. There was no statistical relationship between TS-3'UTR polymorphisms and chemotherapy efficiency (P>0.05). DPYD*5 (T85C), DPYD*9A (A1627G), and TS-5'UTR polymorphisms were significantly associated with chemotherapy efficacy (P<0.05). DPYD*5 (T85C) TC+CC, DPYD*9A (A1627G) AG+GG, and TS-5'UTR 2R3G+3C3G+3G3G carriers showed worse efficacy than DPYD*5 (T85C) TT, DPYD*9A (A1627G) AA, and TS-5'UTR 2R2R+2R3C+3C3C carriers (P<0.05). Unconditional logistic regression analysis revealed DPYD*5 (T85C), DPYD*9A (A1627G), and TS-5'UTR as independent risk factors for 5-FU chemotherapy sensitivity. DPYD*9A (A1627G) and TS-3'UTR polymorphisms failed to show a significant relationship with 5-FU chemotherapy toxicity. DPYD*5 (T85C) and TS-5'UTR polymorphisms were markedly associated with chemotherapy toxicity. Combined detection exhibited a greater impact on patients with toxic side effects (P<0.05). DPYD*5 (T85C), DPYD*9A (A1627G), and TS-5'UTR may be independent risk factors of 5-FU chemotherapy sensitivity. DPYD*5 (T85C) and TS-5'UTR polymorphisms were significantly associated with chemotherapy toxicity. Combined detection exhibited a greater impact on patients with toxic side effects.

Keywords: DPYD, TS, gene polymorphism, advanced colorectal cancer, 5-FU

Introduction

Colorectal cancer (CRC) is the third most common malignant tumor worldwide. In recent years, with the development of the economy and changes in lifestyles, incidence and mortality rates of CRC have significantly increased [1]. In either early surgical intervention or advanced local recurrence and distant metastasis, chemotherapy plays an important role in comprehensive treatment [2-4]. Chemotherapy is a good complement to surgical treatment. It is one of the main treatments for advanced CRC metastasis and recurrence [4, 5]. The colorectal cancer chemotherapy regimen has undergone development from 5-fluorouracil (5-FU) to new chemotherapeutic drugs, including oxaliplatin, irinotecan, capecitabine, and molecular targeted drugs. These drugs have further improved the therapeutic effects of advanced CRC [6]. However, nearly half of the patients are not sensitive to chemotherapy. Most patients with sensitive reactions eventually develop resistance, due to individual differences in chemotherapy

drugs and doses. It was found that genetic factors are one of the main factors affecting efficacy and toxicity levels of drugs [7, 8]. The development direction of cancer treatment includes predicting the responsiveness and toxicity of chemotherapy and selecting a subset of patients that may benefit from the chemotherapy program, as well as targeted individualized treatment according to specific tumor gene phenotypes [9, 10]. Therefore, it is of great clinical significance to search for molecular markers related to chemosensitivity, aiming to screen patients and avoid ineffective and excessive treatment.

In recent years, individualized treatment methods have been widely examined by researchers. The first problem to be solved is the sensitivity of anti-tumor drugs. With a deep understanding of the genetic differences between humans, it was observed that gene polymorphisms are closely related to chemotherapy efficacy [11]. DPD and Thymidylate synthase (TS) are two enzymes that play an important role in the process of cellular nucleic acid metabolism. They interact with 5-FU from different aspects, affecting the efficacy of 5-FU. Thus, they influence the clinical application of 5-Fu chemotherapy in cancer patients. The relationship of DPD and TS gene polymorphisms with chemotherapy efficacy has attracted increasing attention [12, 13]. It was revealed that, in CRC patients, especially advanced CRC, the same 5-FU-based chemotherapy regimen will produce significant differences in efficacy levels for different genotypes [14]. Therefore, it is necessary to explore the relationship of DPD and TS gene polymorphisms with 5-FU chemosensitivity in patients with advanced CRC, aiming to better understand the efficacy of chemotherapy, improve drug efficiency, and reduce severe toxic side effects.

Materials and methods

General information

A total of 100 patients with advanced CRC, in Ganzhou People's Hospital (Ganzhou Jiangxi, China), from January 2017 to December 2017, were enrolled. Patients included 56 males and 44 females. The mean age was 64.57±8.13 (51-77) years old. All patients were diagnosed by histopathological examinations and received fluorouracil-based systemic chemotherapy (including palliative chemotherapy or neoadjuvant chemotherapy). There was no history of other malignant tumors. Karnofsky performance scores (KPS) were greater than 60 points before chemotherapy. Blood routines, as well as liver and kidney function indicators, were within the normal range. ECGs were also normal. Patients received radiotherapy and chemotherapy before exclusion. This study was approved by the Medical Ethics Committee of Ganzhou People's Hospital (Ganzhou Jiangxi, China). All patients provided informed consent.

Sample collection

Fasting peripheral blood (1 mL) was extracted before chemotherapy and stored in anticoagulated EDTA tubes at -20°C. Gender, age, tissue type of colon cancer, metastasis and staging, lifestyle (smoking), past disease history, family history, and other data were collected. Comprehensive physical examinations were performed prior to chemotherapy, assessing chemotherapy tolerance.

Chemotherapy regimen

All patients received FOLFOX4 regimen chemotherapy for at least 2 courses. Some patients received 4-6 courses, according to conditions. During treatment, dosages were adjusted to the conditions and tolerance levels of the patients. Treatment was terminated if serious toxic side effects occurred.

Genome DNA extraction

Genomic DNA was extracted using a DNA extraction kit (DP318, Beijing Tiangen Biochemical Technology Co., Ltd.), according to manufacturer instructions. Concentrations and purity levels of the DNA were measured by a UV spectrophotometer (NANO DROP 1000 Spectrophotometer) and stored at -20°C.

DPYD and TS gene polymorphism detection

Gene polymorphisms of DPYD and TS were detected by PCR amplification (model: ABI 9700 PCR) and Sanger sequencing. Primers were designed by Primer 5.0 and synthesized by Sangon. Primer sequences are shown in **Table 1**. M13 linker was added to both the upstream and downstream primers. Universal M13 sequence was used as the sequencing

Table 1. Primer sequences of DPYD and TS

Gene		Primer sequences
DPYD*5 (T85C)	F	5'-TGTAAAACGACGGCCAGTCCTGGCTTTAAATCCTCGAACA-3'
	R	5'-AACAGCTATGACCATGGCAGTTCTTATCAGGATTTCTTTTCC-3'
DPYD*9A (A1627G)	F	5'-TGTAAAACGACGGCCAGTGAACAAACTGCATAGCAACAATTCTC-3'
	R	5'-AACAGCTATGACCATGTCTCTGTTCTGTTTTGTTTTAGATGGA-3'
TS-3'UTR	F	5'-TGTAAAACGACGGCCAGTCAAATCTGAGGGAGCTGAGT-3'
	R	5'-AACAGCTATGACCATGCAGATAAGTGGCAGTACAGA-3'
TS-5'UTR	F	5'-TGTAAAACGACGGCCAGTAGGCGCGCGGAAGGGGTCCT-3'
	R	5'-AACAGCTATGACCATGTCCGAGCCGGCCACAGGCAT-3'
M13	F	5'-TGTAAAACGACGGCCAGT-3'
	R	5'-AACAGCTATGACCATG-3'

primer. The PCR reaction system contained 10 μL 2 × KOD buffer, 4 μL dNTPs (2.5 mM), 0.5 μL F (10 mM), 0.5 μL R (10 mM), 0.4 μL KOD enzyme, 1 μL DNA, and 3.6 μL H_2O. PCR reaction conditions: Pre-denaturation at 95°C for 5 minutes, followed by 35 cycles of 95°C for 30 seconds, 58°C for 40 seconds, 72°C for 30 seconds, and 72°C for 10 minutes. PCR amplification products were identified by agarose gel electrophoresis and sequenced by Sangon.

Observation indexes

Short term clinical evaluations: Efficacy evaluations were performed according to solid tumor evaluation standards (RECIST) established by the World Health Organization (WHO), including CR, PR, SD, and PD. Effective chemotherapy was defined as CR+PR, while invalid chemotherapy was defined as SD+PD.

Histopathological evaluations: Patients receiving neoadjuvant chemotherapy were divided into four grades, according to the effective criteria of histopathology, 0, I, II, and III. Effective chemotherapy was defined as Grade II+III. Invalid was defined as Grade 0 + Grade I. Toxic side-effects evaluations were performed using WHO-related toxicity grading criteria.

Toxic and side effects assessment: According to WHO standards for classification of acute and subacute chemotherapy toxic effects, adverse reactions over grade III were used as statistical objects.

Statistical analysis

SPSS 11.0 software was used for statistical analysis. Measurement data are expressed as mean ± standard deviation. Enumeration data are depicted as a number or percentage. Moreover, χ^2 tests were employed to analyze whether the SNP genotype distribution was in accord with Hardy-Weinberg equilibrium. Unconditional logistic regression was adopted to analyze the relationship between gene polymorphisms and CRC chemotherapy efficacy and side effects. Odds ratios (OR) and 95% CIs were used to express relative risks. When calculating OR values and 95% CIs, gender, age, and smoking status were statistically corrected as covariates.

Results

DPYD and TS gene polymorphism distribution and genetic balance tests

Genotyping results of 100 patients with advanced CRC are shown in **Table 2**. Moreover, χ^2 tests showed that allele frequency distributions of three single nucleotide polymorphism (SNP) loci were in accord with genetic Hardy-Weinberg equilibrium law (P>0.05), indicating that selected subjects had a population representation.

Correlation of DPYD and TS genotypes with clinical effects of 5-FU

After chemotherapy, 10 patients achieved complete remission (CR), 33 patients achieved partial remission (PR), 28 patients showed stable disease (SD), and 29 patients showed disease progression (PD). Thus, the chemotherapy response rate was 43.00%.

Additionally, χ^2 tests were used to analyze the correlation between genetic polymorphisms and efficacy of 5-FU chemotherapy (**Table 3**).

Table 2. DPYD and TS gene polymorphisms distribution and genetic balance tests

Polymorphic locus	Allele	n (%)	χ^2 value	*P* value
DPYD*5 (T85C)	T/T	84 (84.00)	2.111	0.146
	T/C	14 (14.00)		
	C/C	2 (2.00)		
DPYD*9A (A1627G)	A/A	91 (91.00)	0.222	0.637
	A/G	9 (9.00)		
	G/G	0 (0.00)		
TS-3'UTR	-6/-6	45 (45.00)	2.202	0.138
	-6/+6	39 (39.00)		
	+6/+6	16 (16.00)		
TS-5'UTR	2R2R	8 (8.00)	2.431	0.142
	2R3C	19 (19.00)		
	3C3C	13 (13.00)		
	2R3G	12 (12.00)		
	3C3G	34 (34.00)		
	3G3G	14 (14.00)		

Table 3. Impact of DPYD and TS genotypes on 5-FU efficacy

Variable	n	PR+CR n=43	SD+PD n=57	Efficacy (%) (PR+CR)/n	χ^2	*P* value
DPYD*5 (T85C)					4.570	0.033*
TT	84	40	44	47.62		
TC+CC	16	3	13	18.75		
DPYD*9A (A1627G)					5.658	0.017*
AA	91	43	48	47.25		
AG+GG	9	0	9	0.00		
TS-3'UTR					1.351	0.245
-6/-6 or -6/+6	84	37	32	44.05		
+6/+6	16	6	10	37.50		
TS-5'UTR						
2R2R+2R3C+3C3C	40	24	16	60.00	7.861	0.005*
2R3G+3C3G+3G3G	60	19	41	31.67		

*P<0.05.

Table 4. Unconditional logistic regression analysis of the impact factor of chemotherapy efficacy

Variable	*β*	*SE*	*Wald*	*Sig*	*OR* value	95% *CI*
DPYD*5 (T85C)	1.226	0.492	6.817	0.013	3.406	1.244~6.832
DPYD*9A (A1627G)	1.134	0.513	7.652	0.002	3.107	1.149~8.691
TS-5'UTR	1.047	0.461	7.138	0.008	2.849	1.306~8.073

β: regression coefficient; SE: standard error; Wald: Chi-square value; Sig: *P* value; OR value: odds ratio; 95% CI: 95% confidence interval.

There was no statistical relationship between TS-3'UTR polymorphisms and chemotherapy efficiency (P>0.05). DPYD*5 (T85C), DPYD*9A (A1627G), and TS-5'UTR polymorphisms were significantly associated with chemotherapy efficacy (P<0.05). DPYD*5 (T85C) TC+CC, DPYD*9A (A1627G) AG+GG, and TS-5'UTR 2R3G+3C3G+3G3G carriers showed worse efficacy than DPYD*5 (T85C) TT, DPYD*9A (A1627G) AA, and TS-5'UTR 2R2R+2R3C+3C3C carriers (P<0.05).

Avoiding potential interference from confounding factors, unconditional logistic regression was selected to perform multivariate analysis (**Table 4**). DPYD*5 (T85C) TC+CC, DPYD*9A (A1627G) AG+GG, and TS-5'UTR 2R3G+3C3G+3G3G carriers exhibited lower chemotherapy benefits (P<0.05).

Correlation of DPYD and TS genotypes with 5-FU toxicity

DPYD*9A (A1627G) and TS-3'UTR polymorphisms failed to show a significant relationship with 5-FU chemotherapy toxicity (P>0.05). DPYD*5 (T85C) and TS-5'UTR polymorphisms were markedly associated with chemotherapy toxicity (P<0.05) (**Table 5**).

Correlation between combined DPYD and TS genotype detection and 5-FU toxicity

DPYD*5 (T85C) and TS-5'UTR were combined to detect and predict toxicity of 5-FU. It was observed that DPYD*5 (T85C) TC+CC and TS-5'UTR 2R3G+3C3G+3G3G carriers exhibited heavier 5-FU toxicity (P<0.05) (**Table 6**).

Table 5. Correlation of DPYD and TS genotypes with 5-FU toxicity

Variable	n	Myelosuppression (n, %)	Liver function damage (n, %)	Gastrointestinal reaction (n, %)	Mucosal damage (n, %)
DPYD*5 (T85C)					
TT	84	37 (44.04)	9 (10.71)	39 (46.43)	11 (13.10)
TC+CC	16	10 (62.50)	4 (25.00)	11 (68.75)	6 (37.50)
P value		<0.001	0.006	<0.001	<0.001
OR (95% *CI*)		2.117 (1.052~3.916)	2.778 (1.237~4.151)	2.538 (1.306~4.827)	3.982 (1.568~7.924)
DPYD*9A (A1627G)					
AA	91	43 (47.25)	12 (13.19)	45 (49.45)	15 (16.48)
AG+GG	9	4 (44.44)	1 (11.11)	5 (55.56)	2 (22.22)
P value		0.238	0.062	0.107	0.092
OR (95% *CI*)		0.893 (0.681~2.657)	0.823 (0.714~3.106)	1.278 (0.824~2.173)	1.448 (0.752~3.013)
TS-3'UTR					
-6/-6 or -6/+6	84	39 (46.43)	11 (13.10)	41 (48.81)	14 (16.67)
+6/+6	16	8 (50.00)	2 (12.50)	9 (56.25)	3 (18.75)
P value		0.087	0.124	0.073	0.185
OR (95% *CI*)		1.154 (0.864~1.983)	0.948 (0.562~2.467)	1.348 (0.673~3.041)	1.154 (0.809~3.543)
TS-5'UTR					
2R2R+2R3C+3C3C	40	13 (32.50)	3 (7.50)	12 (30.00)	4 (10.00)
2R3G+3C3G+3G3G	60	34 (56.67)	10 (16.67)	38 (63.33)	13 (21.67)
P value		<0.001	0.013	<0.001	0.007
OR (95% *CI*)		2.716 (1.582~4.374)	2.467 (1.251~3.672)	4.030 (1.968~7.853)	2.489 (1.168~5.249)

Table 6. Correlation between combined DPYD and TS genotype detection and 5-FU toxicity

Variable	*β*	*SE*	*Wald*	*P* value	OR value	95% CI
Myelosuppression	2.083	0.762	8.924	<0.001	4.413	1.824~8.632
Liver function damage	1. 534	0.632	7.248	0.003	3.407	1.104~7.169
Gastrointestinal reaction	1.469	0.527	7.864	<0.001	4.984	1.362~6.703
Mucosal damage	1.417	0.603	6.924	0.026	4.753	1.736~7.284

β: regression coefficient; SE: standard error; Wald: Chi-square value; Sig: *P* value; OR value: odds ratio; 95% CI: 95% confidence interval.

Discussion

Fluorouracil, 5-FU, is a commonly used drug in a variety of tumor chemotherapy regimens. It plays an important role in CRC postoperative and neoadjuvant chemotherapy. Moreover, 5-FU is an anti-metabolic chemotherapeutic drug, a cell-specific drug that mainly acts on the S phase in the cell cycle. The S phase is a key period of DNA synthesis. Therefore, 5-FU mainly reduces protein expression by inhibiting the synthesis of nucleic acids. This, in turn, suppresses tumor cell proliferation and division [15-17]. Although 5-FU does not provide anti-tumor activity, after entering the human body, more than 80% of 5-FU is catabolized by DPD in the liver to form the inactive product dihydrofluorouracil (DHFU). Defective DPD may lead to 5-FU metabolites accumulating toxicity in the body. The remaining drugs are metabolized by 5-fluorouridine triphosphate (FUTP) and 5-fluoro-2-deoxyuracil nucleotide (FdUMP) [1], which can bind with TS and folinic acid (CH2-THF) to form a stable complex. This inhibits TS catalytic activity, affecting DNA synthesis and repair [18]. Therefore, DPD and TS are important target enzymes in the mechanisms of action of 5-FU. Activities of DPD and TS enzyme may directly affect the anti-tumor effects of 5-FU [19, 20].

With the development of the Human Genome Project (HGP) research, researchers have obtained more understanding of gene polymorphisms. It was found that gene polymorphisms change protein expression levels. This, in turn, affects tumor development, radiotherapy and chemotherapy sensitivity, and prognosis. DPD

and TS are key enzymes in the process of cellular nucleic acid metabolism. This can promote intracellular DNA synthesis and cell proliferation and interact with 5-FU in different ways, affecting its efficacy [19]. DPD is encoded by the DPYD gene. More than 40 DPYD mutations have been found with ethnic differences [21]. Incidence of DPYD*2A in Finland and the Netherlands is about 1%. It has not occurred in Han and Japanese populations [22]. DPYD*5 and DPYD*9A have a high frequency of occurrence in all ethnic groups. Liu et al. reported that incidence of DPYD*2A in Chinese Han populations is lower. However, incidence of DPYD*5 polymorphisms was 48.4% and related to survival [23]. Deenen et al. investigated 2,038 cases of American tumor patients receiving fluorouracil-based chemotherapy [24]. The heterozygous mutation of DPYD*2A locus was found in 22 patients. Incidence of adverse reactions decreased from 73% to 28% after reducing the chemotherapy drug dosage. This study observed that incidence rates of DPYD*5 and DPYD*9A in patients with advanced CRC in China were 16% and 9%, respectively. These were lower than the results of Liu [23] and Li [25]. The TS gene 5'-UTR polypeptide repeats also exhibited ethnic differences. Of these, 3R occurred most frequently in Asians. Zou et al. revealed that the TS 3R allele is a risk factor for childhood acute lymphoblastic leukemia [26]. Mo et al. also suggested that TS gene polymorphism may be a risk factor for gastric cancer in Caucasians [27]. The current study found no significant correlation between TS-3'UTR polymorphisms and chemotherapy efficacy ($P > 0.05$). DPYD*5 (T85C) TC+CC, DPYD*9A (A1627G) AG+GG, and TS-5'UTR 2R3G+3C3G+3G3G carriers showed worse efficacy than DPYD*5 (T85C) TT, DPYD*9A (A1627G) AA, and TS-5'UTR 2R2R+2R3C+3C3C carriers ($P<0.05$). Multivariate analysis using unconditional logistic regression showed that DPYD*5 (T85C) DPYD*9A (A1627G) and TS-5'UTR were independent risk factors for 5-FU chemotherapy sensitivity. This study investigated the effects of DPYD and TS polymorphisms on 5-FU chemosensitivity and toxic side effects in patients with advanced CRC, preliminarily analyzing the screening value of gene polymorphisms. Sensitivity-related molecular markers may provide an important basis for clinical individualized treatment of CRC patients. However, the sample size of the current study was quite small. Larger scale studies are necessary in the future.

Conclusion

DPYD*5 (T85C), DPYD*9A (A1627G), and TS-5'UTR may be independent risk factors of 5-FU chemotherapy sensitivity. DPYD*5 (T85C) and TS-5'UTR polymorphisms were shown to be significantly associated with chemotherapy toxicity. Combined detection exhibited a greater impact on patients with toxic side effects.

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Disclosure of conflict of interest

None.

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