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RESEARCH ARTICLE

Dihydropyrimidine Dehydrogenase Gene Variation and Its Association with 5-Fluorouracil Toxicity in Colorectal Patients

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Abstract

Objective: Dihydropyrimidine dehydrogenase (DPD), an enzyme translated by DPD gene (DPYD), has a critical role in the metabolism of 5-fluorouracil (5FU). In this study we aimed to investigate the frequency of the IVS14+1 G>A, 2194G>A, 2846 A>T mutations in the DPYD gene in colorectal cancer patients in north of Iran and their association with side effects of 5FU. **Methods:** Venous blood samples of 89 colorectal cancer patients were drawn. After the DNA extraction from nuclear cells, a polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method was used to detect the frequency of the IVS14+1 G>A and 2846 A>T mutations. Tetra-Primer ARMS PCR optimization method was used to detect the 2194 G>A mutation. Side effects were classified according to CTCAE (common terminology criteria for adverse events V. 4) and the association between different polymorphisms and side effects were evaluated. **Results:** Of 89 colorectal patients, the frequency of IVS14+1 G>A and 2846 A>T polymorphism was 4 (5.1%) and 1 (1.1%), respectively. The 2194 G>A polymorphism was not detected. All 4 patients were heterozygous for IVS14+1 G>A mutation, whereas the only patient with 2846 A>T polymorphism was homozygous. Some adverse effects of 5FU including diarrhea, vomiting, mucositis and stomatitis were more frequent in patients with IVS14+1 G>A polymorphism. **Conclusion:** The prevalence of IVS14+1 G>A mutation in our patients were relatively high and was associated with a higher occurrence of 5FU-associated toxicities.

Keywords: Colorectal cancer- DPYD- IVS14+1G>A- Polymorphism

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Introduction

Colorectal cancer (CRC) is one of the most important causes of cancer-related mortalities worldwide [1]. For more than five decades, 5-fluorouracil (5FU) has been used as an important component of many standard treatments in the multimodal therapy of CRC [2-5]. Identification of patients with an increased risk of development of severe 5FU-associated toxicity would allow either dose-adaptation or the application of new non-fluoropyrimidine-based chemotherapeutic drugs [6].

According to the report of Disease Control Department of Ministry of Health of Iran, in 2007, the fourth highest incidence of all cancers and the second frequent cancer among gastrointestinal tract cancers was related to colorectal cancer [7]. The risk factor like obesity, high meat and fat intake and fiber deficiency are directly related to the incidence of cancer [8-10]. Based on the population-based cancer registry, It has shown that the incidence of colorectal cancer in Iran is between 7 and 8 per 100,000 in both men and women, which are higher than previously reported rates [11].

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The biochemical pathway of 5-FU action and degradation is well stablished and provides 25 genes in which variation might affect 5-FU toxicity but Dihydropyrimidine dehydrogenase (DPD) is initial and rate limiting enzyme in the metabolism of 5-FU. Approximately 80% of 5-FU is metabolized in the liver by Dihydropyrimidine dehydrogenase (DPYD) to dihydrofluorouracil [12].

Lack of DPD gene is a risk factor for developing severe toxicity in treatment by 5-FU drug. Carriers of some alleles such as IVS14+1 G>A, 2846 A>T and 2194 G>A mutation have significantly reduced DPD enzyme levels, resulting in less clearance of 5-FU and such are more likely to develop adverse toxicity following treatment with 5-FU drugs. A number of studies have reported that patients with deficiency in DPD activity may suffer from serious toxicity after the administration of 5-FU. Up to know, more than 30 SNPs (single-nucleotide polymorphisms) and deletion mutation of DPD gene have been found, and the most prevailing one is G to A mutation in the splicing-recognition sequence of intron 14 (known as 14G > A, DPYD*2A) contributing about 50% of the total mutation incidence, this

mutation leads to absence of exon 14, which results in partial or complete deficiency of DPD activity. Some studies have found that 27%-57% of cancer patients with IVS14+1G > A mutation suffered from severe 5-FU-associated toxicity [13- 14]. So, the catabolic route of 5FU plays an important role in the determination of 5FU toxicity [15].

Adverse drug reactions (ADRs) are a major clinical problem and it has been estimated that ADRs were the fourth largest cause of death in the United States after heart diseases, cancer and stroke (16). It is likely that a significant proportion of 5FU-associated toxicities is due to genetically based differences [17-19].

Some research shows that 5-FU induces grade 3 and 4 toxic effect in 20%-30% and toxicity related death in 0.5% patient. Identification of patients at risk of drug induced side effect before 5-FU treatment could enable timely reduction or selection alternative treatment [20].

It has been suggested that a systemic low DPD activity is associated with an increased risk of development of severe 5FU-associated toxicity [21-26]. Using a threshold level of less than 70% of the mean of a control population, 14% of the population would be at risk of developing severe 5FU-associated toxicity [14]. Patients with a partial DPD deficiency proved to have higher risk of developing grade IV neutropenia than patients with a normal DPD activity [14]. Furthermore, in patients with a low DPD activity, the onset of toxicity occurred, on average, twice as fast compared with patients with a normal DPD activity [27]. Considering lack of data regarding the frequency of DPYD polymorphism in our colorectal patients and its association with 5FU-associated toxicity, the aim of this study was to determine three allelic variants of DPYD (IVS14+1 G>A, 2846 A>T and 2194 G>A mutation) and their association with ADRs of chemotherapy regimen containing 5FU in a group of colorectal cancer patients in North of Iran.

Materials and Methods

Eighty-nine colorectal cancer patients who referred to Emam Khomeini Hospital and received 5FU containing chemotherapy regimens were included. Emam Khomeini Hospital is a referral hospital affiliated to Mazandaran University of Medical Sciences, Sari, Iran. The study was approved by ethics committee of the university IR.MAZUMS.REC.95.2480. Two milliliters of venous blood samples were drawn and genomic DNA was extracted from nuclear cells using QIAamp DNA Mini Kit (Qiagen, Germany). A polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method was used to detect the frequency of the IVS14+1 G>A and 2846 A>T mutations applying Mae II and Bse8I restriction enzymes (thermo fisher scientific, USA) respectively as published before [20, 28] and Tetra-Primer ARMS PCR optimization was designed to detect the 2194 G>A mutation (Table 1).

Amplification was performed with an initial denaturation step of 5min at 95°C followed by 35 cycles of 95°C for 1min, 60°C for 1min for IVS14+1 G>A mutation (62°C for 2846 A>T and 58 °C for 2846 A>T mutations), and 72°C for 1min, and finally an extension step of 72°C for 5 min.

Descriptive statistics were used to examine the demographics, clinical characteristics and frequency of different allelic variants of DPYD. Association between allelic variants and adverse reactions of 5FU were compared with Fisher's exact. All acute and late adverse reaction including nausea/vomiting, mucositis, stomatitis, diarrhea and also reactions which occurred following several courses of chemotherapy (e.g., hand-foot syndrome) were recorded. All statistical analysis was performed using SPSS 23. P-values less than 0.05 were considered significant. The procedures were in accordance with the ethical standards of the responsible committee on human experimentation (both institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

Results

Of the 89 cases studied 36 (40.4%) were female and 53 (59.6%) patients were male. The average age of the patients were 56.9 years old. Most patients had colon cancer (59.6%). FOLFOX (71.7%) and FOLFIRI (22.4%) were the most common chemotherapy regimens administered (Table 2). Most patients were in the stage 2 (36%) and stage 3 (25%) of the disease. Metastatic disease was found in 20.2 % of the patients.

All of IVS14+1 G>A polymorphisms found in four patients were heterozygous. The 2846 A>T polymorphism was detected in only one patient. No 2194 G>A polymorphism was found (Table 3). Patients who suffered from side effects with FOLFIRI regimens were more common than FOLFOX regimen. In FOLFIRI regimen, the most common adverse reaction was Hand-Foot Syndrome (HFS) occurred in more than 90% of patients. Diarrhea (32%), vomiting (30%) and mucositis (24%)

Table 1. The Sequences of Primers Used for the Detection of Three Polymorphisms on Dihydropyrimidine Dehydrogenase Gene

Mutation	Forward primer (5'→3')	Reveres Primer (5'→3')	Restriction enzyme
IVS 14+1G>A	TGCAAATATGTGAGGAGGGACC	CAGCAAAGCAACTGGCAGATT	MaeII
2846A>T	AAATGCTGAGTGATATTAATCATTACA	ACCACAGTTGATACACAGATCTTCA	Bse8I
2194G>A	GTCTTGCATAGGTGGTGCCAATGTCA (A allele) AATGCATTTTTCTGGGATGTGAGGGTTT	ACCTGAGACAGTGTTGGTGGCTGTCAC (G allele) GACCTTCTGATTTTTCAGCAACCTCCAA	-

were other adverse reactions experienced by the patients (Table 4). No differences were found in terms of IVS14+1 G>A, 2846 A>T and 2194 G>A polymorphisms and sex of patients. There was a significant association between presence of IVS14+1 G>A polymorphism and some toxicity of 5FU including diarrhea (p=0.041), vomiting (p=0.041), mucositis (p=0.023) and stomatitis (p=0.052). We did not find any correlation between 2846 A>T and 2194 G>A polymorphism and 5FU-associated toxicities (Table 4).

Discussion

In this study, the frequency of three DPYD gene polymorphisms including IVS14+1 G>A, 2846 A>T and 2194 G>A and their association with 5FU-associated toxicity were determined in a group of colorectal cancer patients in North of Iran. The results of our study showed the prevalence of IVS14+1 G>A heterozygote polymorphism was 4.5% and no homozygote form was found. In a similar study in Turkish, Uzunkoy et al reported heterozygous mutations of IVS14+1 G>A in DPYD gene in Turkish population (0.4%) which was less than our study. Also they didn't find any homozygous variant of IVS14+1 G>A, exactly as same as our study [29]. Van Kuilenburg assessed the prevalence of IVS14+1 G>A in 2714 on Dutch patients. Their result showed the prevalence of IVS14+1 G>A polymorphism in DPYD gene was 0.91% (30), less than the amount we found in our study. The other study was conducted on 1702 Caucasian patients, their results showed that the prevalence of heterozygous form of IVS14+1 G>A was 0.94% [31].

Table 2. Demographic and Clinical Characteristics of Patients

Age (years)	
mean	56.9
SD	14.3
Sex, n (%)	
Male	53 (59.6)
Female	36 (40.4)
Diagnosis, n (%)	
Colon	53 (59.6)
Rectum	16 (18)
Colorectal	20 (22.4)
Chemotherapy Regimens; cycles (%)	
FOLFOX	147 (71.7)
FOLFIRI	46 (22.4)
other	12 (5.9)

The difference between the prevalence of polymorphism of IVS14+1 G>A in different population may be associated with different toxicity following 5FU containing regimen. In another study conducted in Taiwan with a similar sample size to our study, Xiaoxiong Wei reported 2.7% of patients had IVS14+1G> A polymorphism in the DPYD gene [32], which was less than the rate of IVS14+1 G>A polymorphism in our study. lower frequency of IVS14+1 G>A polymorphism (1.28%) was reported by Mazzuca in colon cancer patients who were treated with 5FU containing chemotherapy. Among six heterozygous patients, three of them experienced severe side effects, though the relation between polymorphism and 5FU toxicity was not statistically significant. In fact, 89 of 427 patients who did not have IVS14+1 G>A polymorphism also had severed toxicity. In contrast to study of Mazzuca, we observed correlation between IVS14+1 G>A polymorphism and 5FU toxicity [33]. Among three polymorphisms investigated in our study, only IVS14+1 G>A was significantly correlated with diarrhea, mucositis, nausea and stomatitis. Most of patients (75%) with IVS14+1 G>A polymorphism experienced diarrhea and nausea. There was no significant relationship between IVS14+1 G>A polymorphism and other toxicities including vomiting and Hand-Foot Syndrome. The frequency of IVS14+1 G>A polymorphism in some studies were more than the frequency we encountered in our study, though most previous studies reported lower frequency. For instance, Sun and his colleague reported

Table 3. Polymorphism of Dihydropyrimidine Dehydrogenase Gene

Polymorphism	Number of patients	Percent
IVS 14+1G>A		
Yes		
Heterozygous	4	4.5
Homozygous	0	0
No polymorphism	85	95.5
2846A>T		
Yes		
Heterozygous	0	0
Homozygous	1	1.1
No polymorphism	88	98.9
2194G>A		
Yes		
Heterozygous	0	0
Homozygous	0	0
No polymorphism	89	100

Table 4. Adverse Drug Reaction in Patients with IVS 14+1G>A and 2846A>T Polymorphism

Adverse Reaction	IVS 14+1G>A		2846A>T	
	n (%)	P-value€	n (%)	P-value€
Diarrhea	3 (6.3)	0.041	0 (0)	1
Constipation	0 (0)	0.123	1 (1)	1
Nausea	1 (1.8)	0.041	0 (0)	0.561
Vomiting	1 (3.1)	0.497	1 (3.1)	0.402
HFS	4 (2.2)	1	3 (1.6)	1
Mucositis	3 (7.7)	0.023	1 (2.6)	0.473
Stomatitis	3 (5.8)	0.052	1 (1.9)	1

HSF, Hand-foot syndrome, P-value of chi-square test for comparison of side effects between patients with and without the given polymorphism

14% of IVS14+1 G>A polymorphism among patients and its relationship with the incidence of adverse events such as diarrhea, bone marrow suppresses and HFS [34].

The prevalence of 2846 A>T polymorphism in our study was only one case of homozygote type (1.1%). The frequency of 2846 A>T polymorphism which was reported in Seck study was 0.67% among 157 Caucasian patients [35]. We did not find relationship between this polymorphism and 5FU-associated toxicity such as diarrhea. Unlike our study, Deenen et al. reported more than 65% of patients with 2846 A>T polymorphism (63%) complained of diarrhea [36]. It is notable that there is a great variability in both the frequency of 2846 A>T DPYD polymorphism and its association with toxicities. Unlike Deenen study, Carginin et al found that the incidence of diarrhea was only 0.2% in those with a 2846 A>T polymorphism [37]. In our study, we did not detect any significant association between 2846 A>T polymorphism and different toxicities such as nausea, vomiting, mucositis and stomatitis. Froehlich and et al evaluated correlation between DPYD polymorphism and severe toxicity following administration of 5FU. Unlike our study, they found relationship between 2846 A>T polymorphism and severe toxicity [38].

No 2194 G>A polymorphism was found in our study. The results of a study conducted by YF He in 2008 showed that 0.7% of the 142 Chinese patients had 2194 G>A polymorphism, while the presence of this polymorphism was 1.9%, 5.8%, 4.4% in the African-American, Caucasian, and Japanese Populations as like as other polymorphism, there is variability in 2194 G>A polymorphism and its relationship with 5FU-associated toxicities in different studies [32-39].

In conclusion, the prevalence of IVS14+1 G>A mutation in our patients were relatively high and was associated with a higher occurrence of 5FU-associated toxicity especially diarrhea, vomiting, mucositis and stomatitis. The other two investigated polymorphisms, 2846 A>T and 2194G>A, were not associated with 5FU-associated toxicities in our patients.

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Competing Interest

Nothing to declare

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