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Evaluation of Correlation Between Serum Level of Dihydropyrimidine Dehydrogenase Enzyme and Capecitabine Induced Adverse Reaction

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Abstract

Background: Capecitabine is widely used to treat patients with gastrointestinal and breast cancers. However, its narrow therapeutic index is a limitation and prevents the achievement of a good therapeutic response. Dihydropyrimidine dehydrogenase (DPD) is the main enzyme in the metabolism of capecitabine. Previous studies show that deficiency in the activity of this enzyme can lead to incomplete metabolism of fluoroprimidine derivatives and severe complications. However, in the case of capecitabine, limited information based on case reports and small population surveys are available. There is also scarce evidence of a relationship between serum concentrations of DPD and the prevalence of capecitabine adverse reactions.

Objectives: The current study aimed at investigating the relationship between DPD serum concentrations and capecitabine adverse reactions in patients with gastrointestinal tract cancer receiving capecitabine.

Methods: The current cohort study was conducted on 30 patients referred to Isar Clinic affiliated to Mashhad University of Medical Sciences, Iran, diagnosed with gastric or colorectal cancer; treatment with capecitabine-containing regimens including XELOX (capecitabine + oxaliplatin) Or EOX (epirubicin + oxaliplatin + capecitabine) was performed from November 2016 to July 2017. At the beginning of the study, the patients' demographic and laboratory data and information about the type of malignancy and chemotherapy regimen were recorded. Then, on the day before the first chemotherapy course administration until the end of the third cycle of chemotherapy, the side effects of the drug were investigated by interview, clinical examination, and laboratory findings. The occurrence of adverse reactions was assessed based on NCI-CTCAE V4 criteria. The serum concentration of DPD enzyme was measured by the enzyme-linked immunosorbent assay (ELISA) kit and its relationship with incidence of capecitabine induced side effects was evaluated.

Results: A significant relationship was observed between DPD serum concentration and neuropathy ($P < 0.001$), thrombocytopenia ($P = 0.017$), neutropenia ($P = 0.004$), and weakness ($P = 0.014$). However, there was no significant relationship between DPD and other complications. No significant relationship was observed between age and gender of patients and DPD concentration ($P > 0.05$).

Conclusions: According to the data obtained from the current study, the incidence of some of the capectiabine induced complications can be influenced by the serum concentration of DPD.

Keywords: Dihydropyrimidine Dehydrogenase, Capectiabine, Adverse Reaction

1. Background

Capecitabine (Xeloda®) is an oral anti-neoplasm (cytotoxic) chemotherapy medication used to treat patients with gastrointestinal (GI) and breast malignancies. It can be used as monotherapy or in combination with other drugs such as oxaliplatin, irinotecan and cisplatin in GI cancer, and monoclonal antibodies such as trastuzumab (Herceptin®) or bevacizumab (Avastin®) in breast cancer (1). Capecitabine is a relatively safe option in comparison with several other chemotherapy regimens. Its most common side effects include mild to moderate diarrhea, hyperbilirubinemia, stomatitis, hand food syndrome (HFS), and fatigue. Myelosuppresion, abdominal pain, and nausea are also reported. Compared with 5-fluorouracil (5-FU), capecitabine application is associated with less stomatitis, alopecia, neutropenia, diarrhea, and nausea but more HFS (2). The severity of these manifestations depends on

many factors such as types of other combined drugs in regimen, patients' age, and their renal and hepatic function (3). Moreover, the variation of patients' responses and tolerability mostly depends on the relationship between metabolism of capecitabine and genetic differences between individuals. While the anabolic pathway of the metabolism probably mediates the cytotoxic and therapeutic effects, the catabolic one plays an important role in toxicity. Normally, more than 80% of capecitabine is catabolized by a rate limiting enzyme, the first of three enzymes in the flouropyrimidine metabolic pathway, called dihydropyrimidine dehydrogenase (DPD). Its activity varies widely, with most of variability arising from genetic polymorphisms in dihydropyrimidine dehydrogenase (DPYD) gene. A familial state caused by an allelic mutation in the DPYD gene can lead to "DPD deficiency syndrome". The Partial and complete DPD deficiency are reported in 3% - 5% and 0.2% of population, respectively (1, 4). So far 39 different mutations are recognized in the DPD gene (5). This syndrome classically causes early onset and exaggerated toxicity, which clinically presents with mucositis, diarrhea, myelosuppression, HFS, neutropenia, and rarely, but characteristically, neurologic deficits (6). This syndrome is evaluated in different population in several studies. However, to the best of authors' knowledge the correlation of the serum concentration of DPD enzyme and capecitabine induced adverse reactions are not evaluated previously. Only Dong et al., defined the correlation of DPD enzyme serum level and 5-FU induced adverse reactions in 72 patients with colorectal cancer treated with FOLFOX6 regimen. Serum level of DPD was lower in patients with oral mucositis and diarrhea of grade II-IV than in patients with oral mucositis and diarrhea of grade 0-I ($P = 0.016$, $P = 0.047$) (7).

2. Objectives

The current study aimed at evaluating the correlation between serum level of DPD enzyme and capecitabine induced adverse reactions.

3. Methods

3.1. Study Design

The current cohort study was conducted at Isar Center, affiliated to Mashhad University of Medical Sciences, Mashhad, Iran, from November 2016 to July 2017.

3.2. Study Population

Thirty patients with gastric or colorectal cancer diagnosis intended to be treated with the XELOX or EOX regimen for the first time, met the following criteria and were included in the study: Age range 18-70 years, GI tract malignancies (including colorectal and esophagogastric cancers) treated with chemotherapy regimen including capecitabine. Patients with hepatic failure (liver function test (LFT) > 5 times of upper limit normal, or > 3 times of upper limit normal and symptoms), renal failure (glomerular filtration rate (GFR) < 30 mL/minute), and dissatisfaction were excluded from the study.

The XELOX regimen includes capecitabine at a dose of 850 mg/m^2 (1500 mg (three capsules) twice a day) for two weeks followed by one week rest, and oxaliplatin at a dose of 130 mg/m^2 as an intravenous infusion every three weeks in colorectal cancer. The EOX regimen included capecitabine at a dose of 625 mg/m^2 as 1000 mg (two capsules) twice daily for three weeks, and oxaliplatin at a dose of 130 mg/m^2, and epirubicin at a dose of 50 mg/m^2 every three weeks in gastric cancer.

3.3. Ethics

The current study protocol was approved by the local Ethics Committee of Mashhad University of Medical Sciences (IR.MUMS.REC. 1395.27). All participants signed written consent forms.

3.4. Study Protocol

At the beginning of the study, demographic data and other characteristics of patients including age, gender, weight, body surface area (BSA), past medical history, stage of the cancer, and chemotherapy regimen information were collected in a researcher-made form. Patients were reviewed regarding the adverse reaction occurrence at baseline and every three weeks on the day of chemotherapy administration in Isar Clinic, for three courses. Some adverse reactions including GI disorder such as loss of appetite, diarrhea, nausea and vomiting, neuropathy, HFS, and alopecia were evaluated by interview and clinical examination of the patients and using National Cancer Institute common terminology criteria for adverse events version 4 (NCI-CTCAE V4) (8). Some other complaints such as bone marrow suppression and nephrotoxicity were evaluated based on patients' laboratory tests. Moreover, all patients were requested to go to Mana Laboratory from 8:00 AM to 9:00 AM; where whole blood was collected from patients and serum level of DPD enzyme, which is the rate-limiting enzyme in capecitabine catabolism, was defined by the enzyme-linked immunosorbent assay (ELISA) kit (USCN, USA). Blood samples were centrifuged at 1000 rpm for 10 minutes, and then the serum was immediately transferred to a freezer at -70°C, kept until measurement.

Table 1. Demographic and Laboratory Data of the Study Population[a]

	Values
Gender (male: female ratio)	80:20
Age (y)	66.3 ± 5.01
Body weight, (kg)	68.1 ± 10.24
BSA	1.74 ± 0.16
Serum concentration DPD, μg/L	1034.04 ± 217.97

Abbreviations: BSA, body surface area; DPD, dihydropyrimidine dehydrogenase.
[a] Values are presented as mean ± SD unless otherwise indicated.

3.5. Sample Size

Since to the best of authors' knowledge, there was no published study evaluating the correlation between DPD enzyme serum level and capecitabine induced adverse reactions in Iranian population, the current study was defined as a pilot one based on the estimated number of patients with gastrointestinal malignancies referring to Isar Center, treated by XELOX or EOX regimens, the sample size was considered 30 patients.

3.6. Statistical Methods

Results of the current study are shown as mean ± standard deviation (SD) or median (range) for normally and non-normally distributed continuous variables, respectively, and number (percentages) for nominal variables. The Kolmogorov-Smirnov test was used to assess the normality of the variable distributions. Independent samples t test and Chi-Squared test were used respectively to compare normally distributed and nominal variables between the two groups. Pearson correlation and logistic regression tests were used to evaluate correlation between serum level of DPD and different factors; $P < 0.05$ was considered significant.

4. Results

4.1. Characteristics of the Study Population

Thirty patients with colorectal or gastric cancer receiving XEOX or EOX regimen with a mean age of 66.3 ± 5.01 years were enrolled into the study; 80% of the patients were male. Other characteristics of patients are presented in Table 1.

Regarding the type of cancer, 83.3% of patients enrolled in the current study had gastric cancer and 16.7% colorectal cancer. Most of patients in the two groups were in stage 4 of cancer (64% and 80% in gastric and colorectal cancer patients, respectively) (Table 2).

Most of the patients (63.3%) received XELOX regimen and the others received EOX regimen.

Table 2. Stage of Cancer in the Study Population

Cancer Type	Frequency	Percentage
Gastric		
Stage 3	9	36
Stage 4	16	64
Colorectal		
Stage 3	1	20
Stage 4	4	80

Table 3. Capecitabine-Induced Adverse Effects

Adverse Reaction	Frequency (%)
HFS	36.7
Neuropathy	13.3
Diarrhea	33.3
Weakness	73.3
Nausea and vomiting	43.4
Anorexia	63.3
Thrombocytopenia	23.3
Neutropenia	36.7
Hyperbilirubinemia	40
Rise in liver enzymes	13.3

Abbreviation: HFS, hand-foot syndrome.

4.2. Evaluation of Capecitabine Induced Adverse Reactions Based on CTCAE v4

In general, the most common reported side effects during the three courses of chemotherapy were weakness (73.3%), anorexia (63.3%), and vomiting (43.4%) (Table 3).

Deep vein thrombosis occurred in three patients during the study. Two patients experienced nail changes.

Evaluation of the severity of capecitabin induced side effects was conducted at the end of each cycle of chemotherapy based on the CTCAE version 4 scoring system; diarrhea and weakness occurred with highest severity at the end of each course (Table 4). Hyperbilirubinemia also had high prevalence in the three courses of chemotherapy. It should be noted that at the beginning of the study, the score of all evaluated ADRs was zero in all patients.

4.3. Evaluation of the Relationship Between DPD Enzyme Concentration and Patients' Age and Gender and Type of Cancer

According to the results of Pearson correlation test, there was no significant correlation between DPD enzyme concentration and patients' age ($P = 0.89$).

Moreover, regarding the results of the independent samples t test, there was no significant difference in the

Table 4. Distribution of Capecitabine-Induced Side Effects at the End of Each Chemotherapy Cycle[a]

Type of Adverse Effect	End of the First Cycle	End of the Second Cycle	End of the Third Cycle
HFS	0 (1 - 0)	0 (1 - 0)	0 (3 - 0)
Neuropathy	0 (2 - 0)	0 (1 - 0)	0 (1 - 0)
Diarrhea	0 (5 - 0)	0 (5 - 0)	0 (2 - 0)
Weakness	1 (3 - 0)	0 (3 - 0)	1 (3 - 0)
Nausea and vomiting	0 (1 - 0)	0 (5 - 0)	0 (2 - 0)
Anorexia	0 (3 - 0)	0 (2 - 0)	0 (2 - 0)
Neutropenia	3 (10)	0	0
Thrombocytopenia	4 (13.3)	3 (10)	5 (16.7)
Hyperbilirubinemia	6 (20)	6 (20)	12 (40)
Liver function test dysfunction	1 (3.3)	2 (6.7)	2 (6.7)

Abbreviation: HFS, hand-foot syndrome.
[a] Values are presented as median (range) or No. (%).

mean serum concentrations of DPD enzymes between male and female patients (P = 0.52). Serum level of enzyme was compared with independent samples t test between patients with gastric and colorectal cancers and no significant difference was observed between the two groups (P = 0.59).

4.4. Evaluation of the Relationship Between DPD Enzyme Concentration and Capceitabine-Induced Adverse Reactions

Overall, 36.7% of patients experienced different degrees of HFS during three courses of chemotherapy, but based on the logistic regression binary, no significant correlation was observed between the DPD concentration and the incidence of HFS (P = 0.149, r^2 = 0.043).

The same results were observed about neuropathy (P = 0, r^2 = 0.02), nausea and vomiting (P = 0.467, r^2 = 0.075), diarrhea (P = 0.074, r^2 = 0), anorexia (P = 0.149, r^2 = 0.003), and hyperbilirubinemia (P = 0.695, r^2 = 0.008). However, significant correlation was observed between DPD serum concentration and fatigue and weakness occurrence (P = 0.014, r^2 = 0.47), thrombocytopenia (P = 0.017, r^2 = 0.64), neutropenia (P = 0.004, r^2= 0.1), and hepatotoxicity occurrence (P = 0.03, r^2 = 0.51).

5. Discussion

The current study mainly aimed at investigating the relationship between DPD serum concentration and incidence of capecitabine-induced adverse reactions in patients with colorectal or gastric cancer.

In the current study, weakness (73.3%), anorexia (63.3%), and nausea (43.4%) were the most common adverse reactions. There were also two cases of death due to severe diarrhea and one death due to severe nausea and vomiting. Behravan et Al., also investigated common side effects of capecitabine in 109 patients with colorectal cancer, and neutropenia was reported as the most common side effect (20%). In their study, GI complications including diarrhea, and nausea and vomiting were reported as the common side effects (1.5% and 1.3%, respectively) after neutropenia (8). In the current study, nausea and vomiting (43.4%) were among the most common complications, but not diarrhea. However, two deaths due to high degrees of diarrhea were reported. In the study by Shields et al. (9), five patients with diarrhea and dehydration were hospitalized. It seems that the high percentage of cases with complaint of anorexia and vomiting may be related to the course of their disease, not the medication side effects. Three of the patients experienced deep vein thrombosis (DVT) during the study. In some other studies, cardiovascular events such as DVT are reported in patients treated with capecitabine (9).

The capecitabine was better tolerated than 5-FU as mentioned in previous studies, but one of its complications with higher incidence than 5-FU was hyperbilirubinemia (10). It was reported in 40% of patients in the current study. In another study, it was determined that hyperbilirubinemia, diarrhea and HFS were dose-limiting adverse effects of capecitabine monotherapy regimen. Transaminase elevation may occur in therapeutic dose of capecitabine and elevation above five times upper limit normal (ULN) is not common and occurs only in 1% of patients (8). In the current study, transaminase elevation was reported in 16.7% of patients, but none of them were five times above ULN.

The current study found a significant relationship between the incidence of hyperbilirubinemia and the stage of the disease, but no other adverse reactions. In a sim-

ilar study conducted in Iran by Behravan et al., on 109 patients with colorectal cancer receiving a capecitabine, there was no association between the incidence of complications and the stage of the disease (8).

Most of the patients (63.3%) received XELOX regimen followed by EOX regimen (36.7%).

In the current study, there was no significant difference in the incidence of complications in patients receiving these two regimens. In the study by Behravan et al., there were also no differences between the regimens regarding the incidence of complications. Just there was a relatively low difference between capecitabine-based and 5-FU-based regimens. A study conducted in China from 2008 to 2015 compared the efficacy and incidence of adverse effects with XELOX and EOX regimens. The XELOX regimen had significantly less adverse effects and toxicity. Leukopenia, neutropenia, fatigue and weakness, and nausea and vomiting were significantly higher with EOX regimen (11).

In the current study, gender had no effect on the incidence of complications. In the study by Behrovan et al., there was no difference in the incidence of capecitabine-induced complications in patients with colorectal cancer between males and females. It should be noted that all patients in the current study had normal activity of the DPD enzyme.

Some studies found that females were more prone to complications. In a Canadian study on 1093 females and 1355 males receiving 5-FU, the incidence of anorexia, nausea and vomiting, neutropenia, and fatigue were higher among the females (12). The same result was observed in another study on 37 patients (65% females vs. 35% males with normal DPD activity). Patients with breast, colorectal, stomach, and esophageal cancers were included in the mentioned study (13).

In the current study, the serum level of DPD enzyme was measured. The concentration range of the DPD enzyme was 651 - 1502 μg/L. The association of DPD serum level with the side effects of capecitabine was evaluated. There was a significant association between the incidence of neuropathy, weakness and fatigue, thrombocytopenia and neutropenia, and DPD serum concentration. Normally, more than 80% of capecitabine is catabolized by DPD enzyme and it seems that its low serum concentration should result in higher serum concentration of capecitabine and also more incidence of adverse reactions. Limited studies are conducted in this field. A study in China was conducted on the association of DPD serum concentration and 5-FU adverse effects in patients with colorectal cancer. In this study, 72 patients with colorectal cancer treated with FOLFOX6 regimen (including oxaliplatin, folinic acid, and FU) were studied. The concentration of DPD was lower in patients with oral mucositis and diarrhea grades 2 to 4; and in patients with lower DPD concentrations, serum levels of 5-FU were higher and in fact these patients were exposed to higher concentrations of 5-FU. However, no relationship was observed between DPD concentration and response to treatment (14). Another study conducted in China by Ciccolini et al. (15), examined the relationship between the incidence of 5-FU complications and the concentration of DPD in gastric cancer. In this study, 36 patients treated with paclitaxel, leucoverin, and 5-FU were assessed. The DPD serum level was measured by high-performance liquid chromatography (HPLC) method. The activity of DPD enzyme was also measured, and none of the patients had impairment in its function. The concentration range of DPD enzyme in this study was 179.2 - 1589 μg/L, and there was a significant relationship between the incidence of oral mucositis, severe diarrhea, and bone marrow suppression with DPD serum concentration (15).

The relationship between DPD serum concentration and bone marrow suppression was a common finding reported in the study by Pong et al. and the current study as well. No correlation was observed between diarrhea and mucositis and serum level of DPD. Mucositis was not very much prevalent in the current study. Due to the small sample size of all these studies, further studies with larger sample sizes are necessary in this field.

The current study had some limitations. Inappropriate adherence to treatment by some patients due to intolerance of chemotherapy complications such as nausea and vomiting, weakness, and anorexia led to exclusion of some patients from the study. Poor cooperation of patients in answering questions regarding adverse reactions at the end of each chemotherapy course was also problematic.

The above mentioned problems, besides prolonged follow-up period, resulted in a small sample size, which made judgment difficult.

5.1. Conclusions

In the current study, there was a significant relationship between the concentration of DPD enzyme and the incidence of neuropathy, weakness and fatigue, neutropenia, and thrombocytopenia. According to studies conducted worldwide, and the results of the current study, it seems that the side effects of fluoroprimidine agents such as 5-FU and capecitabine are affected by the concentration and activity of DPD enzyme. It is suggested that other studies with larger sample sizes be perform in this field in future.

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Footnotes

Conflict of Interests: Authors declared no conflict of interest.

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