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LETTER

Cardiotoxicity of 5-Fluorouracil and Capecitabine in a Pancreatic Cancer Patient with a Novel Mutation in the Dihydropyrimidine Dehydrogenase Gene

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ABSTRACT

Context 5-fluorouracil (5-FU) is an antimetabolite that acts during the S phase of the cell cycle. Dihydropyrimidine dehydrogenase (DPD) is the initial and rate-limiting enzyme in the pathway that catabolises the pyrimidines. 5-fluorouracil and its oral prodrug capecitabine are used in the treatment of a number of solid tumors, including colorectal, breast, gastric, pancreatic, prostate, and bladder cancers. Common side effects include leukopenia, diarrhea, stomatitis, nausea, vomiting, and alopecia. Cardiotoxicity is a relatively uncommon side effect of 5-fluorouracil and capecitabine. **Case report** This article reports the case of a 63-year-old male with locally invasive pancreatic cancer who developed recurrent chest pain and ischemic electrocardiogram changes after treatment with 5-fluorouracil and capecitabine. Full sequencing of the dihydropyrimidine dehydrogenase (*DPYD*) gene and analysis of the thymidylate synthetase (*TYMS*) gene promoter region was performed. Pharmacogenetic testing revealed p453L (1358C>T) type *DPYD* germ line mutation. This mutation has not been reported previously in association with 5-fluorouracil induced cardiotoxicity. **Conclusion** Cardiotoxicity associated with 5-fluorouracil and capecitabine administration is infrequently reported in the literature and appears to be dose and schedule dependent. Genetic variations such as polymorphic abnormality of *DPYD* are potential causative factors for a significant portion of serious adverse reactions to 5-fluorouracil-based therapy.

Introduction

Fluoropyrimidines have been used as a basic and perpetual part of chemotherapy for malignant tumors. 5-fluorouracil (5-FU) and its pro-drug capecitabine are being widely used in oncology for treatment of various cancers including head and neck, colorectal, breast, and pancreatic tumors [1].

Although capecitabine and 5-FU have comparable end results, capecitabine offers the advantage of convenience as it can be administered orally. Capecitabine is relatively tolerated well in terms of development of known side effects such as diarrhea, neutropenia, and alopecia although causes more cases of severe hand-foot syndrome [2].

Capecitabine (N4-pentyloxycarbonyl-5'-deoxy-5-fluoro-cytidine) is an oral preparation that is metabolized to 5-FU via a three-step enzymatic process. Capecitabine is first hydrolyzed by carboxylesterase in the liver to the intermediate 5'-deoxy-5-fluorocytidine (5'-DFCR) that is later metabolized to 5'-deoxy-5-fluorouridine (5'-DFUR) by cytidine deaminase. 5'-DFUR is finally converted to 5-FU by thymidine phosphorylase [3].

In addition, thymidine phosphorylase is also involved in the activation of 5-FU into fluorodeoxyuridine that will further inhibit the DNA synthesis. Concentration of thymidine phosphorylase is 3-10 times higher in tumor cells compared to healthy tissue. This can enable selective drug activation of 5-FU at the tumor site and limit systemic toxicity [4].

One of the genes considered as potential factors for 5-FU toxicity is the thymidylate synthetase gene (*TYMS*), which is strongly inhibited by 5-FU and considered to be the major drug target. Thymidylate synthetase catalyses the intracellular conversion of deoxyuridylate to deoxythymidylate which is the sole *de novo* source of thymidylate, an essential precursor for DNA synthesis [5]. The active metabolite of 5-FU, 5-fluorodeoxyuridylate (5FdUMP), binds to thymidylate synthetase and inhibits it by forming a stable ternary complex [6].

The human *TYMS* is polymorphic with either double or triple tandem repeats of a 28 base-pair sequence downstream of the cap-site in the 59-terminal regulatory region [7]. The *TYMS* genotype predicts thymidylate synthetase mRNA expression in

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Abbreviations 5'-DFUR: 5'-deoxy-5-fluorouridine; DPD: dihydropyrimidine dehydrogenase; DPYD: dihydropyrimidine dehydrogenase; TYMS: thymidylate synthetase gene; P453L: proline at amino acid position 453

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metastasized colon tumors and normal liver tissue. It is also predicts for response and for toxicity to 5-FU. Patients with the 3R/3R genotype had significantly less response and toxicity, when compared to the 2R/2R or 2R/3R genotypes under 5-FU-based chemotherapy [8].

Finally, 5-FU is catabolized into dihydrofluorouracil by the dihydropyrimidine dehydrogenase (DPD) enzyme that is present in almost all tissues. DPD is the initial rate-limiting enzyme in the catabolism of 5-FU. Polymorphic abnormality of the dihydropyrimidine dehydrogenase (*DPYD*) gene is lately gaining more attention due to its impact on pharmacotherapeutic decisions.

In one study, patients with DPD deficiency experienced profound systemic toxicity in response to 5-FU [9]. The cause of this toxicity seems to be prolonged exposure to 5-FU due to decreased drug catabolism. Recent genetic studies have started to define the mutations in the *DPYD* gene that are responsible for the DPD-deficient phenotype [10]. *In vitro* studies have also shown that *DPYD* over-expression in cancer cell lines confers resistance to 5-FU [11].

In order to reduce effects of *DPYD* variation on 5-FU toxicity, there have been attempts to synthesize new fluoropyrimidine drugs in combination with drugs that inhibit DPD activity [12]. By controlling DPD activity, a new class of fluorinated pyrimidines has been developed to minimize the variability of 5-FU pharmacodynamics, to decrease 5-FU toxicity, and improve its efficacy. Recently, these drugs, referred to as DIFs (DPD inhibitory fluoropyrimidines), have brought a new era of oral 5-FU therapy [13].

Milano *et al*. [14] have found a significant but weak relationship between peripheral blood mononuclear cells-DPD activity and FU clearance (r=0.31), which emphasizes the need to individualize therapy and dosing appropriately.

On the other hand, few studies described a limited role for polymorphic abnormality of *DPYD*, especially the IVS14 + 1 G>A mutation, in 5-FU related toxicity [15, 16, 17]. Two recent studies also concluded that *DPYD* promoter hypermethylation is not of major importance as a prognostic factor for severe toxicity in 5-FU based chemotherapy [15, 18].

Cardiotoxicity is an unusual life-threatening side effect of 5-FU. Myocardial infarction, sudden death, unstable angina, hypotension, and pulmonary edema are most common side effects, which have been reported. Vasospasm is the most commonly suspected hypothesis as the primary mechanism of inducing cardiotoxicity. These symptoms were often observed during the late phase of administration of the drug [18, 20, 21]. Other studies also concluded that cardiotoxicity is schedule dependent [22, 23].

To date, studies showing the need to mandate routine screening for *DPYD* or *TYMS* mutations are lacking. Also, relationship between polymorphic abnormality of *DPYD* and 5-FU induced cardiotoxicity is unclear. We report a case of 5-FU and capecitabine induced cardiotoxicity in a patient with a novel polymorphic abnormality of *DPYD*.

Patient and Methods

A 63-year-old male was diagnosed with locally advanced pancreatic carcinoma. His past medical history was significant for coronary artery disease status post stent placement, deep venous thrombosis following left arthroscopic knee surgery status post inferior vena cava filter placement, history of anthracosis status post right lobectomy, chronic back pain, gout, and tobacco abuse 10 pack/year. He quit smoking one year ago.

His medication list was consistent of aspirin, colchicine, amlodipine, isosorbide mononitrate, clopidogrel, metoprolol, sublingual nitroglycerin, oxycodone, and docusate. He was occasionally drinking alcohol. His family history was significant for coronary artery disease in several family members with one case of premature cardiac death.

Abdominal CT scan showed infiltrative changes at the tail of the pancreas and at the distal transverse colon. Air fluid levels are noted within large bowel without extension to the small bowel. A fairly high grade obstruction was noted on the distal transverse colon. There is thickening of the anterior renal fascia and mild stranding around the left kidney. The liver and adrenal glands are unremarkable. The gallbladder fossa shows no abnormal findings. The kidneys show no calculi present. There is no retroperitoneal lymph node enlargement. CA 19-9 level was 1,458 U/mL (reference range: 0-29 U/mL).

He was initially treated with continuous infusion of 5-FU and radiotherapy. Treatment was complicated with fever, thrombocytopenia, and development of chest pain requiring hospital admission and cardiac evaluation.

Dipyridamole stress test was performed and showed left ventricle ejection fraction of 58%. Perfusion defect due to ischemia cannot be totally excluded and apparent defect in the inferior wall was interpreted as attenuation artifact. However, the electrocardiogram changes associated with dipyridamole infusion was strongly indicative of severe underlying coronary artery disease.

Echocardiogram showed a normal left ventricle size and contractility, normal aorta, right atrium, and mitral valve. It also showed mild pulmonic regurgitation and a mildly dilated left atrium. Subsequently, he underwent cardiac catheterization with placement of three stents and continued radiation therapy.

5-FU was replaced with capecitabine. After one week of treatment, he developed recurring chest pain and later switched to gemcitabine twice weekly. He was able to complete radiotherapy and three weeks of gemcitabine and had tolerated the medication well.

Subsequently, he was tested for polymorphic abnormality of *DPYD* and *TYMS* with TheraGuide 5-FU™ (Myriad Genetic Laboratories, Inc., Salt Lake City, UT, USA) pharmacogenetic test.

Results

Analysis consists of PCR and DNA sequencing of all 23 coding exons and approximately 690 adjacent intronic base pairs of the *DPYD* gene. PCR and DNA sequencing analysis is also used to report the number of 28 base pair repeats within the 5'UTR region at the *TYMS* gene.

Patient was found to be heterozygous for P453L (1358C>T) type *DPYD* germ line mutation. This mutation is predicted to result in the substitution of leucine for proline at amino acid position 453 (P453L) thus, disrupting the normal structure and function of the DPD. The proline normally found at this codon position is also evolutionarily conserved. This novel missense mutation has not been reported previously in association with 5-FU induced cardiotoxicity.

TYMS analysis identified the 2R/3R genotype. In previous studies patients with this genotype have no increased risk of 5-FU toxicity compared to the general population [8, 24, 25].

Discussion

Polymorphic abnormality of *DPYD*, a known pharmacogenetic syndrome associated with 5-FU

Table 1. Polymorphisms of *DPYD*.

Reference	Genotype	Nomenclature	Allele Frequency
Ridge *et al*., 1998 [40]	IVS14+1G>T	*DPYD**2A	0
Celik *et al*., 2002 [41]	IVS14+1G>T	*DPYD**2A	0.75%
Wei *et al*.,1996 [42]	IVS14+1G>T	*DPYD**2A	2.7%
Van Kuilenburg *et al*., 2005 [43]	IVS11+1G>T	-	Unknown
Van Kuilenburg, 2004 [28]	100del A	-	Unknown
Seck *et al*., 2005 [44]	295-298delTCAT	*DPYD**7	0.003%
Yamaguchi *et al*., 2001 [45]	812delT	-	0.46%
Van Kuilenburg *et al*., 2002 [46]	1039-1042delTG	-	Unknown
Ridge *et al*., 1998 [40]	1897delC	*DPYD**3	0
Van Kuilenburg, 2004 [28]	61C>T	-	Unknown
Hsiao *et al*., 2004 [47]	1156G>T	*DPYD**12	0
Hsiao *et al*., 2004 [47]	62G>A	-	0
Yamaguchi *et al*., 2001 [45]	74A>G	-	0.46%
Seck *et al*., 2005 [44]	85T>C	*DPYD**9A	3.7%
Van Kuilenburg *et al*., 2002 [46]	257C>T	-	Unknown
Seck *et al*., 2005 [44]	496A>G	-	0.08%
Ezzeldin *et al*., 2003 [48]	545T>A	-	Unknown
Van Kuilenburg *et al*., 2002 [46]	601A>C	-	Unknown
Van Kuilenburg *et al*., 2002 [46]	632A>G	-	Unknown
Vreken *et al*., 1997 [49]	703C>T	*DPYD**8	Unknown
Van Kuilenburg *et al*., 2005 [43]	731A>C	-	Unknown
Ezzeldin *et al*., 2003 [48]	775A>G	-	Unknown
Hsiao *et al*., 2004 [47]	1003G>T	*DPYD**11	0
Ogura *et al*., 2005 [50]	1097G>C	-	Unknown
Van Kuilenburg *et al*., 2002 [46]	1108A>G	-	Unknown
Ezzeldin *et al*., 2003 [48]	1217T>C	-	Unknown
Seck *et al*., 2005 [44]	1218G>A	-	0.01%
Van Kuilenburg *et al*., 2002 [46]	1475T>C	-	Unknown
Seck *et al*., 2005 [44]	1601G>A	*DPYD**4	0.14%
Wei *et al*.,1998 [51]	1627A>G	*DPYD**5	35.2%
Yamaguchi *et al*., 2001 [45]	1627A>G	*DPYD**5	0.46%
Van Kuilenburg *et al*., 2005 [43]	1651G>A	-	Unknown
Johnson *et al*., 2002 [10]	1679T>G	*DPYD**13	Unknown
Yamaguchi *et al*., 2001 [45]	1714C>G	-	0.46%
Wei *et al*.,1998 [51]	2194G>A	*DPYD**6	6.7%
Seck *et al*., 2005 [44]	2194G>A	*DPYD**6	0.02%
Ogura *et al*., 2005 [50]	2303C>A	-	Unknown
Ezzeldin *et al*., 2003 [48]	2329G>T	-	Unknown
Vreken *et al*., 1997 [49]	2657G>A	-	Unknown
Seck *et al*., 2005 [44]	2846A>T	-	0.006%
Ezzeldin *et al*., 2003 [48]	2921A>T	-	Unknown
Van Kuilenburg *et al*., 2002 [46]	2933A>G	-	Unknown
Vreken *et al*., 1998 [52]	2983G>T	*DPYD**10	Unknown
Seck *et al*., 2005 [44]	3067C>T	-	0.003%
Seck *et al*., 2005 [44]	1236G>A	-	0.003%
Yamaguchi *et al*., 2001 [45]	1896T>C	-	9.8%

toxicity, has been detected in 3% to 5% of the population. This abnormality and DPD deficiency can be identified by genetic analysis and obtaining DPD levels in the peripheral blood mononuclear cells, respectively [26].

DPYD is the gene that codes for dihydropyrimidine dehydrogenase. There are at least 34 types of *DPYD* variants reported to date (Table 1). The mutation IVS14 + 1 G>A, DPYD*2A is the most common mutation associated with clinical DPD deficiency [27]. This mutation was detected in 24-28% of all patients suffering from severe 5-FU toxicity [28]. Screening for this mutation may identify up to 60% of individuals with absolute DPD deficiency who are at greatest risk of toxicity [29]. Down regulation by methylation of the *DPYD* promoter region has been identified as one of the more important regulatory mechanisms of DPD enzymatic activity [30]. Although resistance to 5-FU depends on many factors, tumoral DPD activity is a determining factor in predicting 5-FU-responsiveness [31].

Cardiotoxicity associated with 5-FU administration is infrequent. Recently, Spasojević *et al*. [32] have performed an *ex vivo* and *in vivo* study of the effects of cisplatin and 5-FU on erythrocytes, using a variety of biophysical techniques. Their research showed 5-FU provoked a pronounced decrease of the O_2 level in blood and affected the metabolism of phosphate compounds, while cisplatin had no such effects. They suggested decreased oxygen transfer capacity of erythrocytes as a cause of 5-FU related ischemia.

In one study [22], 17 of 427 patients treated with 5-FU developed clinical symptoms and electrocardiographic abnormalities indicating 5-FU cardiotoxicity. Patients with continuous infusion of 5-FU had a higher incidence of cardiotoxicity. Seven of the 17 patients with 5-FU cardiotoxicity had an acute myocardial infarction, 4 developed ischemic changes, while 4 more patients had—electrocardiographic abnormalities consistent with coronary vasospasm, of whom one subsequently died.

De Forni *et al*. [33] showed 28 of 367 patients receiving high dose 5-FU had cardiac events with only nine of them having cardiac history. Six of these patients' cardiac symptoms returned to baseline but eight had unstable angina, eleven had hypotension, one had pulmonary edema and four had sudden death.

In another study of 1350 patients without any cardiac history [34], 5-FU administration induced chest pain in 10 patients including an infarct like pattern in two (with one death), heart failure in one patient, angina pain without electrocardiographic changes in three patients and electrocardiographic changes without any symptoms in two patients. These symptoms seem to have resolved upon discontinuation of treatment, except for one patient who died later of a cardiac infarct. This suggests that cardiotoxicity can happen even in patients with no significant cardiac history.

Jensen *et al*. [35] reviewed cardiotoxicity among 668 patients treated with 5-FU or capecitabine for gastrointestinal cancers and concluded 5-FU induced cardiotoxicity is only related to cardiac and renal co-morbidity. They suggested in this situation, rechallenge with modified 5-FU-based chemotherapy regimen supported by symptomatic medical treatment is feasible. Unfortunately, pharmacogenetic testing was not performed in any of these studies.

Although 5-FU associated cardiotoxicity is not clearly understood, polymorphic abnormality of *DPYD* is theorized as a plausible cause. Milano *et al*. [36] reported one case of 5-FU related cardiotoxicity in 19 patients with polymorphic abnormality of *DPYD* (5%).

There have been reports of capecitabine related cardiotoxicity. Toxicity with this drug ranged a wide spectrum with different mechanisms, from coronary vasospasms [37] to acute coronary syndrome [38]. Frickhofen *et al*. [39] reported a case of acute coronary syndrome following treatment of both 5-FU and capecitabine. They have recommended against using this prodrug if a previous toxicity with 5-FU has been observed.

Conclusion

Association between *DPYD* variants and 5-FU related cardiotoxicity is unclear. Adequate predictive models and pharmacogenetic testing should be identified to establish a possible relationship between 5-FU and capecitabine induced cardiotoxicity and polymorphic abnormality of *DPYD.*

Previously unreported P453L (1358C>T) mutation as a novel *DPYD* variant which is observed in the context of 5-FU related cardiotoxicity represents an interesting candidate for further studies.

Conflict of interest The authors have no potential conflicts of interest

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