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Case Report

Initiation of *DPYD* Testing-Site Case Study

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Abstract

The Dihydropyrimidine Dehydrogenase (DPD) enzyme mainly in the liver catabolizes Fluoropyrimidines, e.g, 5-FU and its oral pre-prodrug capecitabine. Decreased DPD activity increases the risk of severe toxicity, which may be caused by a single nucleotide polymorphism in the DPD enzyme-coding gene *DPYD*. *DPYD* is a large and highly polymorphic gene with several hundred reported genetic variants, but only a few are linked to DPD activity. The prevalence of DPD deficiency in the population is 3-5%. The four most commonly studied *DPYD* variants are *DPYD**2A, *DPYD**13, c.1236G>A/HapB3 and c.2846A>T. In our clinic, a patient received adjuvant capecitabine treatment after a successful colon cancer operation. She developed severe toxicity within just a couple of days from the start of the first cycle and died despite active treatments and several days in intensive care. Posthumously, *DPYD* gene analysis was performed, and she was found to carry a heterozygous pathogenic variant (c.1905+1G>A (*DPYD**2A)). This case prompted the initiation of *DPYD* gene testing in our clinic as a routine practice for all patients who were scheduled to start fluoropyrimidine-based chemotherapy. During this period, many patients with heterozygous variants with significantly decreased enzyme activity were found, as well as one homozygous *DPYD* variant, *DPYD**2A, with zero DPD activity. The patient was withheld from adjuvant chemotherapy, follow-up was initiated, and the patient is currently without relapse. In conclusion, all patients should be routinely tested for DPD activity by genotyping (i.e. *DPYD* gene test) and/or phenotyping (i.e. DPD enzyme activity) before starting fluoropyrimidines.

Keywords: 5-FU; Capecitabine; Case report; Dihydropyrimidine dehydrogenase; *DPYD*

Introduction

Fluoropyrimidines, including 5-fluorouracil and its oral pre-prodrug capecitabine, are the most widely used antineoplastic agents in the treatment of colorectal, pancreatic, gastric, breast, and head and neck cancers [1]. They are used as single agents or in combination with other anti-neoplastic agents (e.g. epirubicin, irinotecan, oxaliplatin, taxanes) in neoadjuvant, adjuvant and metastatic setting. However, in 10-30% of patients, the use of fluoropyrimidines can cause severe adverse events [2], most commonly including non-bloody diarrhoea, mucosal ulceration, neutropenia and hand-foot syndrome. In 0.5-1% of patients, severe side effects may result in mortality [3].

Intolerance of fluoropyrimidines is mostly associated with deficiency of the enzyme dihydropyrimidine dehydrogenase (DPD), which plays a key role in the catabolism of 5-FU. It is the rate-limiting enzyme and degrades over 80% of the drug to its inactive metabolite 5-fluoro-5,6-dihydrouracil (FUH2) [4]. The gene *DPYD*, which consists of 23 exons on chromosome 1p21.3, encodes DPD. More than 160 single nucleotide polymorphisms (SNPs) have been identified within this gene, some of which result in altered enzyme activity [5]. Strategies for testing DPD deficiency are based on either genotyping *DPYD* or measurement of the DPD phenotype. *DPYD* variants may result in absolute (0.5% of the population) or partial (3-5% of the population) DPD deficiency [6,7]. Therefore, the prevalence of DPD deficiency in the population is approximately 3-5% [6,7]. Approximately 50-88% of patients carrying a variant in *DPYD* suffer from grade >III fluoropyrimidine-related toxicity. The clinically most relevant

polymorphisms are *DPYD**2A (c.1905+1G>A; IVS14+1G>A; rs3918290), *DPYD**13 (rs55886062, c.1679T>G, 1560S); c.1236G>A/HapB3 (rs56038477, E412E); and c.2846A>T (rs67376798, D949V) [8-10]. Three meta-analyses were performed, which confirmed the strong association between the abovementioned four variants and fluoropyrimidine toxicity [11-13].

There are individual dosing guidelines provided by The Dutch Pharmacogenetics Working Group (DPWG) [14] and the Clinical Pharmacogenetics Implementation Consortium (CPIC) [15]. Genotype-guided dosing has been shown to not have a negative effect on the effectiveness of fluoropyrimidine-based chemotherapy, resulting in significantly improved patient safety [16]. In addition, it has been reported that *DPYD* variant screening and genotype-guided dosing can be cost-saving strategies [17], and in March 2020, the European Medicines Agency (EMA) safety committee recommended that patients should be tested for the lack of the DPD enzyme before starting cancer treatment with drugs containing fluoropyrimidines [18]. This recommendation has been a turning point for the routine use of DPD deficiency testing, based on genotype and/or phenotype, in most clinics. Although it is becoming a routine practice, the type of the test varies widely from one clinic to another in Finland. Some of the clinics only look for the four common pathogenic genotypic variants that have strong clinical evidence. However, this does not give a complete picture, as it does not provide information on enzyme activity. Therefore, it has been suggested that the enzyme activity and the level of uracil (a substance broken down by DPD) be measured in the blood [19,20]. In this paper, we will present the process of the initiation of *DPYD* testing in our clinic and our experience. We started testing before the EMA gave their recommendation, as we had a patient (Case 1) with fatal adverse effects after capecitabine administration. The initiation of the testing led to the identification of a patient (Case 2) with a homozygous *DPYD**2A variant and complete deficiency of DPD enzyme activity. Through these cases we will describe our experience of routinely initiating *DPYD* testing in detail.

Case 1

A 64-year-old woman had a history of hypertension, aortic insufficiency and seropositive rheumatoid arthritis. A colonoscopy was performed in spring 2018 as the patient had irregular bowel movements and blood in the stool. She was diagnosed with a circular tumour obstructing the lumen of the sigmoid colon. The biopsy confirmed the diagnosis of invasive adenocarcinoma. Body CT scan was performed to rule out distant metastases. Thus, in April 2018, she underwent left hemicolectomy and lymphadenectomy, and a report by a pathologist confirmed grade I pT3N1bM0 adenocarcinoma of the sigmoid colon. During recovery, perforation of the jejunum occurred and was treated by laparotomy with segmental intestinal resection.

In June 2018, the patient visited the oncology clinic, and based on the stage of the disease, we planned adjuvant treatment with CAPOX for 6 cycles and then capecitabine for 2 cycles. During that time, we did not have a routine practice of testing for *DPYD* gene mutations before starting 5-FU-based treatment. Therefore, the patient had started the first cycle of CAPOX as planned with a dose reduction of 20% because of concerns regarding post-operative infection and rheumatoid arthritis. On day 3, she started to have grade 2 diarrhoea, and on day 4, she developed grade 3 oral mucositis, which led to difficulty swallowing. On day 5, the patient contacted our clinic, and capecitabine treatment was withheld on day 5. On day 6, the patient was hospitalized as the symptoms worsened. The blood count revealed leukopenia 2.16 (E9/L), but the patient was afebrile. We immediately started rehydration therapy and antibiotic prophylaxis (piperacillin/tazobactam 4 g x 3 i.v. and moxifloxacin 400 mg x 1 i.v.). Due to the development of neutropenia, we started filgrastim 30 MU s.c. In addition, the patient was put on parenteral nutrition (Nutriflex lipid 1250 ml/day), as the patient could not eat because of severe mucositis. On day 12, bone marrow suppression worsened. The neutrophils were as low as 0.00, and thrombocytes were 18. Because of bone marrow suppression, Solu-Medrol 40 mg x 2 i.v. was started. On day 16, prophylactic caspofungin was started to treat probable opportunistic fungal infections. Neutrophil levels continued to be 0.00. Due to thrombocytopenia, the patient received several thrombocyte infusions. On day 18, the patient was drowsy and unresponsive to stimulus, followed by seizures. The medical emergency team on call tended to the patient right away and administered lorazepam i.v. The patient was hypertensive with blood pressure levels above 210/110 mmHg. She was given Catapressan 150 µg i.m, and Albetol infusion was started. An MRI of the brain revealed diffuse posterior hyper-intensive activity and haemorrhagic changes, suggesting posterior reversible encephalopathy syndrome (PRES). As per the Glasgow coma scale, her consciousness level was 3. She was intubated and put on non-invasive ventilation to support her respiration. The consciousness level continued to be the same on day 24. To rule out status epilepticus, an EEG was performed, which showed generalized irritation without any epileptic activity.

On day 26, the situation remained the same. Neutrophils were still as low as 0.01, and thrombocytopenia was 10. CRP levels increased from 288 to 418, although the patient was still afebrile. Blood culture was performed, and based on the consultation of infectious diseases specialist, the antibiotics were changed to a broader spectrum (Meronem 1gx3i.v. and vancomycin 1gx2i.v.), and caspofungin was continued. Despite adequate treatment, CRP increased to 370 on day 28, and diarrhoea continued, often mixed with blood. Body CT scan was performed to identify the infection focus. On the right side of the lung, there was pleural effusion and related atelectasis. Ileus in the small bowel was observed without signs of perforation. As per the advice of the gastrosurgeon, a nasogastric tube was placed to alleviate the ileus symptoms. Taking

the entire situation into consideration, it was decided to withhold operative management of the ileus. On day 33, she had an episode of paroxysmal atrial fibrillation that turned into sinus rhythm with amiodarone infusion. Her level of consciousness remained unchanged, and a control brain MRI was taken, which showed that the PRES changes were being alleviated. Although the radiological situation seemed better, the clinical situation deteriorated. We had a discussion with the patient's relatives about the entire situation, and taking into account that the patient was unresponsive to the given treatment, we mutually decided not to resuscitate her if the situation demanded it. On day 34, the creatinine levels rose, and the patient developed metabolic acidosis. On day 38, she was febrile. Thrombocyte and haemoglobin levels decreased rapidly. However, at this point, neutrophils rose to levels of 2.75. Due to prolonged intubation and worsening stomatitis, tracheostomy was performed on day 38. On day 41, haemoglobin dropped from 83 to 65, and the patient suffered from bloody diarrhoea. Clinically, we suspected gastrointestinal bleeding; the patient was prepared for gastroscopy. However, unfortunately, her condition worsened further, and she died on day 42. An autopsy was performed that showed signs of diffuse bone marrow necrosis, but there were also signs of cells, suggesting recovery of the bone marrow. There were also signs of fungal infections in the kidneys, thyroid glands, central nervous system and bone marrow. In both lungs, there were signs of pneumonia. In the right basal ganglion of the brain, there were haemorrhagic and ischaemic changes. In the small intestine, bleeding and signs of ischaemia were observed. There were no metastases. The reason for death per the forensic medicine specialist was determined to be bone marrow depression caused by chemotherapy. Retrospectively, we performed an analysis of the *DPYD* gene, and a heterozygous pathogenic variant (c.1905+1G>A (*DPYD**2A)) was found, which is the most well-studied mutation associated with DPD. This was the major turning point in our clinic that made *DPYD* testing a routine practice before starting 5-FU-based treatments.

Case 2

Previously, a 67-year-old female had taken medications for hypertonia and had diabetes of adult onset and hypercholesterolaemia. She was a current smoker, and her alcohol use was modest. At the beginning of 2020, she started to suffer from rectal pain and bleeding, and colonoscopy revealed a very distal rectal adenocarcinoma. Rectal MRI showed a cT4cNX tumour with suspicion of the involvement of the mesorectal fascia, and a body CT scan showed no metastases. At diagnosis, blood chemistry indicated that haemoglobin was 127 g/l and leucocytes, neutrophils and alkaline phosphatase were slightly elevated. Alanine aminotransferase, creatinine, bilirubin, sodium, potassium and CEA were normal. According to the guidelines, chemoradiation with 5-fluoropyrimidines (capecitabine was planned) was the pre-operative treatment of choice. However, the test for *DPYD* revealed total deficiency (homozygous genotype *DPYD**2A/*2A) of function of the enzyme, and therefore, i.v. 5-fluorouracil and p.o. capecitabine or tegafur/gimeracil/oteracil were contraindicated. In patients with total deficiency of *DPYD*, the combination of trifluridine-tipiracil (FTD/TPI) is feasible because the elimination pathway of these compounds does not use *DPYD*. However, due to the lack of clinical evidence and safety regarding the use of FTD/TPI concomitantly with long-course irradiation given as a treatment for rectal cancer and the contraindication to the use of 5-fluoropyrimidines, chemoradiation in this patient was omitted, and she received a short pre-operative 5x5 Gy irradiation. Delayed laparoscopic abdominoperineal excision and permanent colostomy were performed eight weeks after the cessation of radiotherapy. Histology showed grade 2 ypT2 adenocarcinoma without lymph node involvement (0/12 nodes) or signs of lymphovascular and perineural invasion, and the radiotherapy treatment effect was estimated to be minimal. No adjuvant chemotherapy was given due to the contraindication of the use of 5-fluoropyrimidines as monotherapy or in combination with oxaliplatin. At the first follow-up, CEA was normal. The homozygous *DPYD**2A variation was further confirmed by the DPD enzyme activity measurements. The patient had no detectable DPD activity in mononuclear cells, and the uracil levels were extremely high in both plasma (59.33 µmol/l, normal reference value 0-1 µmol/l) and urine (1891 µmol/l, normal reference value 0-18.1 µmol/l).

Materials and Methods

DPYD genotype

For *DPYD* genotyping, we used three different methods and analysis laboratories. In Case 1, only formalin-fixed paraffin-embedded tissue (FFPE) was available for gene analysis. Thus, the DNA was extracted with a commercial extraction kit in Jyväskylä Central Hospital and further sequenced in the BluePrint Genetics laboratory with the *DPYD* single gene test. For Case 2, the first gene analysis was performed in the Helsinki University Hospital Genetics Laboratory, where homozygous variation was found. However, as this analysis covers only the *DPYD**2A variation, we further confirmed the gene results by analysing the patient samples a second time in the Amsterdam UMC, Laboratory of Genetic Metabolic Diseases, the Netherlands. Their method is based on DNA Sanger sequencing, including all coding exons plus flanking intron sequences, as described previously [21]. In addition, the analysis of the relative copy numbers of the coding exons of the *DPYD* gene was performed using multiplex ligation-dependent probe amplification (MLPA) [21].

DPD phenotype

The DPD phenotype of Case 2 was analysed through both DPD enzyme activity measurement and the measurement of

uracil concentrations in plasma and urine [22]. All these analyses were conducted at the Amsterdam UMC, Laboratory of Genetic Metabolic Diseases, the Netherlands.

Discussion

The two typical colon cancer patients presented here had planned to have adjuvant capecitabine therapy. There were no symptoms or other indications available to suspect DPD deficiency. Case 1 initiated capecitabine adjuvant therapy and was admitted to the hospital after taking capecitabine for a short time. She had typical symptoms of DPD deficiency syndrome after fluoropyrimidine treatment, and she died 6 weeks later in the hospital. Case 1 occurred in 2018, when no *DPYD* test was in clinical use in Finland. Case 2 occurred two years later, when the *DPYD* test was used, which detected homozygous *DPYD* mutations and completely deficient DPD enzymes. The patient did not receive adjuvant fluoropyrimidines and is now under follow-up without any relapse. Adjuvant treatment is given to reduce risk of relapse, and in metastatic setting patients may survive several years with current treatments. DPD testing offers a valuable tool to avoid toxic treatment-related deaths in patients with homogenous variants, or health compromising toxicity in patients with pathological of heterogeneous variants, recommended to receive fluoropyrimidine-based chemotherapy. In case of partial DPD deficiency, a dose reduction at least 50% is required. This has been explored in prospective trials and seems feasibly to take in practice [23]. In case of complete DPD deficiency, fluoropyrimidines are to be omitted, and by current chemotherapy guidelines for adjuvant setting, there is no schedule to offer these patients. Statistically, if 8 patients out of 100 will not receive adjuvant fluoropyrimidine-based chemotherapy, 4 of them will avoid toxicity-related death, and the other 4 will have reduced risk of severe side-effects. On the other hand, if the risk of relapse after radical colorectal cancer surgery is 10-40%, and if adjuvant therapy reduces the risk by 50%, 5-20 patients receiving adjuvant chemotherapy should not relapse. However, if 8 % of these 20 patients (i.e. 1.6 patients) are by DPD testing recognized ineligible to receive adjuvant fluoropyrimidines, these 1.6 patient are in 5-20% risk for relapse, while 8 patients will be spared from extreme toxicity including 4 treatment-related deaths among them (1.6 vs. 8 patients). Thus, *DPYD* tests have distinct benefits for patients over adjuvant therapy, and those patients with *DPYD* test results indicating pathological heterozygous variants should receive dose reductions, while those with homogenous variants should not receive adjuvant therapy at all.

Routine *DPYD* testing was initiated at Vaasa Central Hospital [24] three years ago, and thereafter Finnish cancer centers have taken up the upfront screening as a routine. In the beginning, the use of phenotype testing or *DPYD* gene test was limited despite of the evidence of linking *DPYD* variants to severe toxicity. In France, uracil phenotype testing had become mandatory, and it was required to get the fluoropyrimidine drug from pharmacy. This phenotype testing is sufficient to define the most of severe DPD deficiencies for the decision not to administer fluoropyrimidines at all. Further testing of *DPYD* variants may resolve variant composition and appropriate dose reductions to be done. Also, Denmark was among the first countries that recommended *DPYD* testing before administrating fluoropyrimidines. Earlier, the obstacles for routine upfront *DPYD* testing have been the price of the test and its unavailability in many countries. Furthermore, none of the medical companies has demanded testing, and it has not been a requirement in fluoropyrimidine labels, other than warnings of risk for fatal side-effects as a characteristic of this class of cancer drugs. This has now changed, as in March 2020 the safety committee of European Agency of Medicine gave a recommendation that patients should be tested for lack of DPD before administrating of fluoropyrimidines. Manufactures are also urging testing. Our real-world data is supporting the importance of DPD deficiency testing, as 8% of our patients had class 5 heterozygous *DPYD* variant [24]. Furthermore, our results show the complexity of the DPD deficiency, as alone *DPYD* genotype or DPD phenotype testing were not precise enough for definitive conclusions or the results were not fully congruent. Literature often states that clinically there are four most relevant variants that should be tested. However, based on our data and confirmed by phenotype analysis, we had missed 29% of patients with pathogenic variants by testing only these four [24].

As a conclusion we recommend a workflow as follows: first test the *DPYD* genotype with gene variant analysis (this covers all the known pathogenic variants), and second measure the enzyme activity. Based on both of these results the decisions on medication and dose reduction can be done.

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