Published in final edited form as:

Clin J Oncol Nurs. 2014 October ; 18(5): 581–585. doi:10.1188/14.CJON.581-585.

5-Fluorouracil Toxicity and Dihydropyrimidine Dehydrogenase Enzyme: Implications for Practice

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Case Study

A 71 year old Caucasian male has a history of an unknown primary cancer by pathology, with initial diagnosis in 2011. He has a presumptive diagnosis of either metastatic pancreatic adenocarcinoma or cholangiocarcinoma. The patient started treatment with dexamethasone, oxaliplatin, irinotecan, 5-fluorouracil (5-FU) as part of the FOLFIRINOX regimen. He received his first cycle. Four days after receiving chemotherapy the patient was admitted to the hospital for intractable nausea, vomiting, and abdominal pain.

On admission, an abdominal series, electrocardiogram and cardiac enzymes were all within normal limits and the patient was started on intravenous (IV) antiemetics and fluids for supportive care. Five days after admission, the patient was noted to be neutropenic and was placed on broad-spectrum antibiotics prophylactically after being pancultured. Over the next 2–3 days the patient began exhibiting subtle signs of confusion. A computed tomography (CT) scan of the head showed no evidence of abnormalities. His blood counts recovered 10 days later but had worsening confusion and encephalopathy, despite his cultures being negative.

A repeat CT of the head and magnetic resonance imaging (MRI) of the brain continued to show no abnormal findings. Neurology and psychiatry were then consulted and the patient was thought to have a non-localizing encephalopathy. The patient then became completely encephalopathic to the point where he was found to be in a catatonic state. Multiple laboratory test, including a thyroid stimulating hormone (TSH) level, and B12, which were all within normal limits. His ammonia level was the only test noted to be slightly elevated. The patient was then treated with lactulose for approximately 4 days unfortunately, with no improvement in mental status. After some discussion with his primary oncologist, the patient was tested for the dihydropyrimidine dehydrogenase (DPD) enzyme activity. A blood sample was taken and sent to a laboratory in Utah. The patient was found to have a heterozygous dihydropyrimidine gene mutation (DYPD), IVS14+1G>A *DPYD* variant (DPYD*2A), the most common gene mutation. He was therefore presumed to have 5-FU

toxicity secondary to the inability to effectively metabolize 5-FU due to this enzyme deficiency.

A family meeting was initiated and the patients' prognosis was discussed at length with the patient's wife and sons. It was decided by all involved, that the patient would be discharged to a long-term care facility until he recovered. A hospice consult was also initiated. The patient died a year later, but never recovered from his encephalopathy.

Introduction

Dihydropyrimidine Dehydrogenase and 5-FU

5-Fluorouracil is a fluorinated pyrimidine analogue, which is commonly used in combination chemotherapy regimens for treating common solid tumors such as colorectal, breast, lung, and head and neck cancers (Cordier et al., 2011). Its' major metabolite is 5-fluoro-2'-deoxyuridine-5'-monophosphate which inhibits the enzyme, thymidylate synthase which results in the depletion of intracellular thymidylate pools and leads to cessation of deoxyribonucleic acid (DNA) synthesis (Ezzeldin & Diasio, 2004; van Kuilenburg, 2004). In addition, 5-Fluorouracil is also metabolized to ribose and deoxyribose triphosphate metabolites that misincorporates into ribonucleic acid (RNA), and DNA causing cell death decreasing tumor burden (Ezzeldin & Diasio, 2004; van Kuilenburg, 2004).

For effective catabolism and clearance of 5-FU, the enzyme dihydropyrimidine dehydrogenase, which is encoded by the dihydropyrimidine gene, plays an important role (Ezzeldin & Diasio, 2004; van Kuilenburg, 2004; A. B. P. van Kuilenburg et al., 2012). Eighty to ninety percent of 5-Fluorouracil is cleared metabolically in the liver, while the rest is excreted in the urine. The clearance of 5-FU is mediated by a series of enzymes including dihydropyrimidine dehydrogenase (Saif, Syrigos, Mehra, Mattison, & Diasio, 2007; A. B. van Kuilenburg et al., 2001). Dihydropyrimidine dehydrogenase is the initial rate limiting enzyme, in the catabolic pathway of 5-FU (Etienne et al., 1995; Milano & McLeod). Therefore, any alteration in this sequence of enzymatic activity can lead to toxic accumulation of 5-FU (Ezzeldin & Diasio, 2004; Saif et al., 2007; van Kuilenburg, 2004; A. B. P. van Kuilenburg et al., 2012).

Dihydropyrimidine dehydrogenase deficiency occurs in 3–5% of the overall population (Borràs et al., 2012; Etienne et al., 1995; Morrison, Bastian, Dela Rosa, Diasio, & Takimoto, 1997; Yen & McLeod, 2007). The reduced activity of the enzyme increases the half-life of the drug, resulting in excess accumulation of the drug and subsequent toxicity (Amstutz, Froehlich, & Largiader, 2011; Borràs et al., 2012; Etienne et al., 1995; Morrison et al., 1997). Cancer patients with a complete or near complete deficiency of the dihydropyrimidine dehydrogenase enzyme suffered from severe toxicity, which may even cause death after administration of 5-Fluorouracil (A. B. van Kuilenburg et al., 2001; van Kuilenburg, Meinsma, Zoetekouw, & Van Gennip). The most common loss of function allele of the dihydropyrimidine gene (DYPD) is the splice-site mutation c.1905+1G>A, DPYD*2A, which leads to deficiency of the enzyme (Amstutz et al., 2011; A. B. van Kuilenburg et al., 2001; van Kuilenburg et al.). Other less common variants associated with dihydropyrimidine dehydrogenase deficiency and grade 3 or greater 5-fluorouracil toxicity in case controlled

studies include: c.1679T>G; c.2846A>T; c.496A>G; c.1905+1G>A; c.1679T>G; c.234-123G>C; and c.1129-923C>G (Amstutz et al., 2011).

Diagnosis

Unfortunately, due to small percentage (3–5%) of the population with the dihydropyrimidine dehydrogenase enzyme deficiency, testing is not readily available, and routine screening is not recommended (Borràs et al., 2012; Etienne et al., 1995; Morrison, Bastian, Dela Rosa, Diasio, & Takimoto, 1997; Yen & McLeod, 2007). However, if a patient is suspected of having the DPYD gene mutation, testing may be done by utilizing several methods.

The principal method used by many hospitals and oncologic practices is the enzymatic radioassay to determine the activity of DPD. This is done by a polymerase chain reaction (PCR) test to detect the DPYD gene mutation. The most common gene mutation analyzed for is the DPYD*2A (A. B. van Kuilenburg et al., 2012).

Another test is the Ribonucleic acid (RNA) extract from peripheral blood mononuclear cells by radioassay, and measurement of DPD mRNA copy number by PCR assay can also be used. If however, the patient is neutropenic, the DPD-deficiency may be done by genetic analysis using denaturing high performance liquid chromatography (Johanna, Chingying, Yung-Kang, & Carlo, 2012). This test also analyses for the most common mutation DPYD*2A (A. Van Kuilenburg et al., 2001).

The third test is a rapid 2-¹³C-uracil breath test. Scientist believe that this test may be applied in most clinical settings if successfully validated, since the other test used are time-consuming, labor intensive and not found in many facilities. The test analyses breathe samples after ingesting aqueous 2-¹³C for the DPD deficiency. If this test can be validated in the future, its' impact can be profound on patient outcomes as more patients can be more readily screened for DPD enzyme deficiency (Mattison et al.). However, until it passes more rigorous testing, this technique is still under experimentation.

Testing for the DPD enzyme deficiency can be done at various commercial laboratories thorough the United States. In most cases, a test kit can be ordered or a blood sample sent to a qualified laboratory. However, there are only few companies that conduct testing for different genetic mutations of the DPYD gene. Most laboratories only test for the most common mutation DPYD*2A (Table. 1).

Clinical Manifestations

Deficiencies in the dihydropyrimidine dehydrogenase enzyme has been shown to cause severe 5-FU drug-related toxicities, including grade 3 or greater. In many cases, toxicity usually requires extensive medical intervention since most cases are usually diagnosed after the administration of one cycle of 5-fluorouracil as was noted in our case study (Ezzeldin & Diasio, 2004).

The clinical presentation of 5-fluorouracil toxicity may include fever, mucositis, stomatitis, nausea, vomiting, and diarrhea. Neurologic abnormalities such as cerebellar ataxia and changes in cognitive function can also be seen but only less than one percent of the

population (Cordier et al.). These are often subtle at first, and may then lead to significant changes in level of consciousness such as a severe coma. Other symptoms such as leukopenia, neutropenia, and possibly thrombocytopenia and anemia are also common in patients with 5-FU toxicities. In some cases, rare incidences of severe skin rashes may occur (Saif et al., 2007).

Management

Management of suspected severe 5-fluorouracil toxicity associated with the DPD deficiency should include discontinuation of the any further administration of 5-FU. Other methods suggested by the review of the literature include the utilization of hemodialysis and hemoperfusion to rapidly remove any remaining drug from the body (Ezzeldin & Diasio, 2004; Morrison et al., 1997). However, in some cases where patients have normal renal function, the drug is rapidly eliminated from the body and does not require this intervention.

Other alternative methods include the administration of pyrimidine nucleosides such as thymidine or uridine (Ezzeldin & Diasio, 2004; Morrison et al., 1997). The administration of thymidine or uridine works by overcoming the block in thymidylate synthesis. However, it is recommended that thymidine not be administered within 12 hours immediately following 5-FU administration because the thymidine formed can decrease 5-FU clearance (Morrison et al., 1997). However, the efficacy of pyrimidine nucleosides such as thymidine or uridine has had mixed results in the literature and has not been proven to be fully effective. These treatments have not been approved by the Food and Drug Administration.

However, aggressive, holistic, supportive care is the mainstay of treatment at present (Ezzeldin & Diasio, 2004; Morrison et al., 1997). Treatment for these patients should include antiemetics to manage nausea and vomiting, intravenous fluid and electrolyte support for severe diarrhea and mucositis, pain medications to effectively treat pain, and appropriate broad spectrum antibiotic and antifungal medications coverage for infection prophylaxis. The management and treatment of 5-FU induced encephalopathy remain unclear (Table 2). Treatment strategies mainly include supportive measures (Cordier et al.). Some cases discussed in the literature have seen benefit with the use of a thiamine infusion and corticosteroids, but they have not shown consistent efficacy (Takimoto et al., 1996). As noted in our case study, lactulose was administered due to elevated ammonia levels, but no symptomatic improvements in the patients' mental status were seen. In some cases, the patient may also need to be admitted to the intensive care unit as close monitoring may be required.

Colony stimulating growth factor can be administered to boost white blood counts in patients with 5-FU toxicity, who have severe neutropenia. It has mostly been used in cases where there is 5-FU toxicity associated with febrile neutropenia. However, this also has questionable results for patients with 5-FU toxicity, as it has shown little benefit in improving patient outcomes (Ezzeldin & Diasio, 2004). It is recommended that patients be pancultured to rule out infection prior to administering growth factors. In certain cases, diagnostic imaging such as chest x-rays may also be required to make an accurate diagnosis.

Discussion

In the United States alone, thousands of fatalities occur each year due to severe adverse drug reactions. In fact, it is estimated that of the 2 million patients that receive 5-FU more than 30% of these patients exhibit some form of toxicity related to 5-FU (Wu, Bell, & Wodchis, 2012). It is also noted that of this population, more than 50% of these patients have the DPD enzyme deficiency (Mattison et al.). Although it is difficult to clinically diagnose the DPD deficiency at an early onset, it is imperative that a cost effective, screening method for DPD deficiency is developed for better patient outcomes.

Advanced Oncology Practitioners and Oncology nurses must be especially vigilant in recognizing 5-FU toxicity to improve patient outcomes (Morrison et al. 1997). A comprehensive medical history must be done to infer if there is a patient or family history of any adverse drug reactions to 5-FU or other agents and a thorough assessment and examination should occur prior to each treatment cycle. Patients and families should also be fully informed about both the common and adverse side effects of 5-FU-based therapy. In addition, nursing staff should be more educated on the existence and adverse side effects of severe 5-FU toxicity associated with dihydropyrimidine deficiency for prompt medical intervention (Morrison et al., 1997).

Oncology Practitioners must therefore be cognizant of the fact that a comprehensive physical assessment is always required when treating patients, in addition to a broad knowledge of pharmacology. The importance of pharmacogenetic correlations in the treatment of patients could potentially determine a patients' overall quality of life and prolonged survival.

Supportive care is indicated and still continues to be the standard of care for patients with 5-FU toxicity. Therefore, it is also important to educate patients and their caregivers on the importance of early recognition of adverse side effects. Patients and caregivers should immediately notify the treating healthcare provider and any further administration of 5-FU should be discontinued. It is also imperative that adverse reactions be treated at an early stage to prevent further medical complications for patients (Table 2).

Conclusion

Cost effective screening tests for the dihydropyrimidine dehydrogenase gene mutation and its' variants associated with 5-FU drug metabolism are greatly needed in the clinical setting to improve patient outcomes (Borràs et al., 2012). Early determination of DPD activity and DYPD mutation by radioassays would allow for enhanced detection and identification of patients at high risk, ultimately giving clinicians the ability to select more appropriate treatment modalities for patients and improve overall outcomes (Amstutz et al., 2011; Cédric & Joseph). Unfortunately, since guidelines and more efficient screening tools are a futuristic approach for patients with the DPD deficiency at this time, early recognition is of vital importance. Future research in this area should include development of clinical guidelines and effective and low cost screening methods.

Implications for Nursing

Good patient assessment and education are imperative to early treatment of 5-FU induced toxicity. Oncology practitioners should thoroughly educate patients and their caregivers on both the common and adverse side effects of 5-FU-based therapy, and when it may be necessary to immediately contact their healthcare provider. Patients should also be closely monitored and tested if they are thought to have the DPD enzyme deficiency. Any further administration of 5-FU should be discontinued. Nursing research should also focus on educational strategies to effectively teach nurses and practitioners about 5-FU toxicity associated with dihydropyrimidine deficiency, as early recognition of these signs and symptoms can improve patient outcomes.

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Table 1**Testing for 5-FU Toxicity Associated with DPD Deficiency**

Test	Specifications
5-FU toxicity and chemotherapeutic response panel	<ul style="list-style-type: none"> • PCR, single nucleotide extensions, fragment analysis • Whole blood • Only detects targeted mutations in the DPYD and TYMS genes • Cost: \$560 • Results: 10–14 days
DPD 5-FU toxicity	<ul style="list-style-type: none"> • Only detects the presence of the wild type or mutant allele for the IVS14+1G>A mutation • PCR, restriction enzyme digestion, gel electrophoresis • Whole blood or buccal swab kit • Cost: \$441 • Results: 72 hours
DPD enzyme assay	<ul style="list-style-type: none"> • Test isolates the peripheral blood mononuclear cells from the blood specimen and performs the DPD enzyme assay • Whole blood • Only tests for the IVS14+1G>A mutation • Cost: \$400 • Results: About 3 business days
<i>DPYD</i> gene mutation analysis	<ul style="list-style-type: none"> • Only detects the IVS14+1G>A mutation • PCR • Whole blood (5 ml) • Cost: \$500 • Results: 7 days
IVS14+1G>A genotyping reagents for gel electrophoresis	<ul style="list-style-type: none"> • Simple and reliable PCR assay detects IVS14+1G>A • Can be performed in less than two hours • Simple setup and interpretation • 50 reaction test kit • Cost: \$2,500 per kit
Theraguide testing	<ul style="list-style-type: none"> • Comprehensive test offering full sequencing of DPYD, as well as analysis of the TYMS gene • Whole blood • Test kit available • Cost: \$1,175 • Results: Within 7 days

5-FU—5-fluorouracil; DPD—dihydropyrimidine dehydrogenase; PCR—polymerase chain reaction

Note. Based on information from ARUP Laboratories, 2013; EntroGen, Inc., 2013; Individualized Treatment Technology Laboratories, 2013; Integrated Genetics, 2014; Quest Diagnostics, 2013.

Table 2**Symptoms and Interventions for 5-FU Toxicity**

Symptom	Interventions
Diarrhea	<ul style="list-style-type: none"> • Loperamide: A loading dose of 4 mg, followed by 2 mg orally every four hours is the standard first-line therapy • Octreotide: 100 mcg subcutaneous three times per day for three days, followed by 50 mcg three times per day for three days • Opium tincture • Cholestyramine
Encephalopathy	<ul style="list-style-type: none"> • Guidelines are unclear on treatment modalities • Obtain labs (blood glucose, thyroid function tests, ammonia levels) • Supportive measures • Reduce next chemotherapy dose and infusion rate • Use of corticosteroids or thiamine (efficacy not proven)
Mucositis	<ul style="list-style-type: none"> • Basic oral care • Saline mouth rinses 4–6 times per day • Pain medications • Oral cryotherapy (30 minutes) in patients receiving 5-FU • Keratinocyte growth factor-1 40 mcg/kg per day for three days may be useful in patients receiving bolus 5-FU plus leucovorin
Myelotoxicity	<ul style="list-style-type: none"> • Antibiotic prophylaxis • Antifungal prophylaxis • Antiviral prophylaxis • Contact precautions for all patients known to be colonized or infected with multi-drug resistant organisms • Hand hygiene with alcohol sanitizer • Influenza vaccinations • Prophylactic colony-stimulating factors
Nausea and vomiting	<ul style="list-style-type: none"> • Aprepitant (NK-1 RA) • Cannabis and cannabinoids • Granisetron or ondansetron (5-HT₃ RA) • Palonosetron (5-HT₃ RA) • Single-dose fosaprepitant (NK-1 RA) • Dexamethasone • Benzodiazepine
Skin reactions	<ul style="list-style-type: none"> • Apply topical wound care if blistering and ulceration develop (if recommended by physician or dermatology consultation) • Instruct patients to wear sunscreen and protective clothing during sun exposure

5-FU—5-fluorouracil; 5-HT₃—5-hydroxytryptamine; NK—natural killer; RA—receptor antagonist

Note. Based on information from the Oncology Nursing Society, 2014.