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

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Digital Object Identifier: 10.1188/14.CJON.581-585

Key words: chemotherapy; quality of life; supportive therapies

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5-fluorouracil (5-FU) is a fluorinated pyrimidine analog, which is commonly used in combination chemotherapy for treating solid tumors. Dihydropyrimidine dehydrogenase plays an important role in catabolism and clearance of 5-FU. Any alteration in that sequence of enzymatic activity can lead to toxicity and even death in some patients. The most common loss of a functional allele of the dihydropyrimidine gene is the splice-site mutation c.1905+1G>A, which leads to deficiency of the enzyme. However, because of the small percentage of the population in which the deficiency occurs, routine screening is not recommended, and commercial testing is costly. Treatment measures for 5-FU toxicity are mainly supportive, including palliation of symptoms. Good patient assessment and education are imperative to early treatment of 5-FU–induced toxicity. Advanced oncology practitioners and oncology nurses 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.

Dihydropyrimidine dehydrogenase (DPD) and 5-fluorouracil (5-FU) is a fluorinated pyrimidine analog, which is commonly used in combination chemotherapy regimens for treating solid tumors in cancers such as colorectal, breast, lung, and head and neck (Cordier et al., 2011). The major metabolite is 5-fluoro-2-deoxyuridine-5'-monophosphate, which inhibits thymidylate synthase, resulting in the depletion of intracellular thymidylate pools and cessation of DNA synthesis (Ezzeldin & Diasio, 2004; van Kuilenburg, 2004). In addition, 5-FU is metabolized to ribose and deoxyribose triphosphate metabolite, which breaks down into RNA and DNA, causing cell death and decreasing tumor burden (Ezzeldin & Diasio, 2004; van Kuilenburg, 2004). The enzyme DPD plays an important role in effective catabolism and clearance of 5-FU (Ezzeldin & Diasio, 2004; van Kuilenburg, 2004; van Kuilenburg et al., 2012). Eighty to ninety percent of 5-FU is cleared metabolically in the liver, whereas the rest is excreted in the urine. The clearance of 5-FU is mediated by a series of enzymes including DPD (Saif, Syrigos, Mehra, Mattison, & Diasio, 2007; van Kuilenburg, Muller, et al., 2001). DPD is the initial rate-limiting enzyme in the catabolic pathway of 5-FU (Etienne et al., 1995; Milano & McLeod, 2000). Therefore, any alteration in this sequence of enzymatic activity can lead to a toxic accumulation of 5-FU (Ezzeldin & Diasio, 2004; Saif et al., 2007; van Kuilenburg, 2004; van Kuilenburg et al., 2012).

DPD deficiency occurs in 3%–5% of the population (Borràs et al., 2012; Etienne et al., 1995; Morrison, Bastían, 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 and subsequent toxicity (Amstutz, Froehlich, & Largiader, 2011; Borràs et al., 2012; Etienne et al., 1995; Morrison et al., 1997). Patients with cancer who have a complete or near complete deficiency of the DPD enzyme suffer from severe toxicity, which may cause death after administration of 5-FU (van Kuilenburg, Muller, et al., 2001). The most common loss of functional allele of the dihydropyrimidine (DPYD) gene is the splice-site mutation c.1905+1G>A, which leads to deficiency of the enzyme (Amstutz et al., 2011; van Kuilenburg, Muller, et al., 2001).
### TABLE 1. Testing for 5-FU Toxicity Associated With DPD Deficiency

<table>
<thead>
<tr>
<th>Test</th>
<th>Specifications</th>
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| 5-FU toxicity and chemotherapeutic response panel | - 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                 | - 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                  | - 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 |
| *DPYD* gene mutation analysis     | - 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 | - 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                | - 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


al., 2001; van Kuilenburg, Van Lenthe, et al., 2001). Other less common variants associated with DPD deficiency and grade 3 or greater 5-FU 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). Other genetic variances may also contribute to 5-FU toxicity, including *CHST1* rs9787901 and *GSTM3* rs1799735 polymorphisms (Rumiato, Boldrin, Amadori, & Saggioro, 2013).

### Diagnosis

Testing for the DPD enzyme deficiency can be completed at various commercial laboratories throughout the United States. In most cases, a test kit can be ordered, or a blood sample can be sent to a qualified laboratory. However, few companies conduct testing for different genetic mutations of *DPYD*, and most laboratories only test for the most common mutation, c.1905+1G>A (see Table 1). Because of the small percentage of the population in which the deficiency occurs and because commercial testing is costly, routine screening is not recommended (Borràs et al., 2012; Etienne et al., 1995; Morrison et al., 1997; Yen & McLeod, 2007). However, if a patient is suspected of having the *DPYD* gene mutation because of his or her unusual reaction to 5-FU, testing may be done by using one of several methods. The principal method used by many hospitals and oncologic practices is the enzymatic radioassay to determine the activity of DPD, which uses a polymerase chain reaction (PCR) test to detect the *DPYD* mutation (van Kuilenburg et al., 2012).

RNA extracted from peripheral blood mononuclear cells by radioassay measures *DPYD* messenger RNA copy number by PCR assay. If the patient is neutropenic, DPD deficiency testing may be done by genetic analysis using denaturing high-performance liquid chromatography because these patients are more at risk for infections, and, therefore, any type of invasive procedures may not be recommended (Sistonen, Smith, Fu, & Largiadèr, 2012). This test also analyzes for c.1905+1G>A (Van Kuilenburg et al., 2001).

An additional test is a rapid 2-13C-uracil breath test. If shown to accurately test for the DPD enzyme, scientists believe a 2-13C-uracil breath test could be applied in most clinical settings because the other tests used are time consuming, labor intensive, and not found in many facilities. The test analyzes breath samples after ingesting aqueous 2-13C and evaluates for the DPD deficiency. If this test can be validated in the future, it may profoundly affect patient outcomes because more patients can be screened for DPD enzyme deficiency (Mattison et al., 2004). However, until it passes more rigorous testing, this technique is still considered experimental.

### Clinical Manifestations

Deficiencies in the DPD enzyme have been shown to cause grade 3 or greater 5-FU drug-related toxicities. In many cases, toxicity usually requires extensive medical intervention because most cases are diagnosed after the administration of one cycle of 5-FU (Ezzeldin & Diasio, 2004).

The clinical presentation of 5-FU 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 occur in less than...
Aprepitant (NK-1 RA)

Loperamide: A loading dose of 4 mg, followed one percent of the population (Cordier et al., 2011). These are often subtle at first, but may then lead to significant changes in level of consciousness, such as a severe coma. Other symptoms, such as leukopenia, neutropenia, thrombocytopenia, and anemia, are also common in patients with 5-FU toxicities. Skin rashes and photosensitivity are less common (Saif et al., 2007).

Management

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

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 thymidylate synthesis. Thymidine should not be administered within the 12 hours immediately following 5-FU because the thymidine formed can decrease 5-FU clearance (Morrison et al., 1997). The efficacy of pyrimidine nucleosides, such as thymidine or uridine, have had mixed results and have not been demonstrated to be fully effective (Morrison et al., 1997). Uridine, by itself, is not adequately absorbed when administered orally. Visturonidine, has been designed to overcome the delivery problem of uridine. This drug is efficiently absorbed by the intestine into the blood and converted to uridine (von Borstel, O’Neil, & Bamat, 2009).

Aggressive, holistic, supportive care is currently the mainstay of treatment (Ezzeldin & Diasio, 2004; Morrison et al., 1997). Treatment should include antiemetics to manage nausea and vomiting, IV fluid and electrolyte support for severe diarrhea and mucositis, pain medications to effectively treat pain, and appropriate broad-spectrum antibiotic and antifungal medications for infection prophylaxis. The management and treatment of 5-FU-induced encephalopathy remain unclear. Treatment strategies mainly include supportive measures and palliation of symptoms (Cordier et al., 2001) (see Table 2). Thiamine infusion and corticosteroids may offer some benefit, but they have not shown consistent efficacy and no recent literature was found to support their use (Takimoto et al., 1996). As noted in the case study, lactulose was administered because of elevated ammonia levels, but no symptomatic improvement in the patients’ mental status was seen. In some cases, the patient may need to be admitted to the intensive care unit, because close monitoring may be required.

Colony-stimulating growth factors can be administered to boost white blood counts in patients with 5-FU toxicity and severe neutropenia. They have mostly been used in cases of febrile neutropenia but have shown little benefit in improving morbidity and mortality (Ezzeldin & Diasio, 2004). Patients should be punculated to rule out infection prior to administering growth factors and broad-spectrum antibiotics. 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 because of severe adverse drug reactions (Wu, Bell, & Wodchis, 2012). Of the two million patients that receive 5-FU, an estimated 30% of those patients exhibit some form of toxicity related to 5-FU (Wu et al., 2012). More than 50% of patients with severe 5-FU-related toxicities have the DPD enzyme deficiency (Mattison et al., 2004); therefore, a cost-effective

<table>
<thead>
<tr>
<th>TABLE 2. Symptoms and Interventions for 5-FU Toxicity</th>
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<tbody>
<tr>
<td><strong>Symptom</strong></td>
<td><strong>Interventions</strong></td>
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<tr>
<td>Diarrhea</td>
<td>Loperamide: A loading dose of 4 mg, followed by 2 mg orally every four hours is the standard first-line therapy. Ocarte: 100 mcg subcutaneous three times per day for three days, followed by 50 mcg three times per day for three days</td>
</tr>
<tr>
<td></td>
<td>Opium tincture Cholesteramine</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>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)</td>
</tr>
<tr>
<td>Mucositis</td>
<td>Basic oral care Saline mouth rines 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.</td>
</tr>
<tr>
<td>Myelotoxicity</td>
<td>Antibiotic prophylaxis Antifungal prophylaxis Antiviral prophylaxis Contact precautions for all patients known to be colonized or infected with multidrug-resistant organisms Hand hygiene with alcohol sanitizer Influenza vaccinations Prophylactic colony-stimulating factors</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>Aprepitant (NK-1 RA) Cannabis and cannabinoids Granisetron or ondansetron (5-HT, RA) Palonosetron (5-HT, RA) Single-dose fosaprepitant (NK-1 RA) Dexamethasone Benzodiazepine</td>
</tr>
<tr>
<td>Skin reactions</td>
<td>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.</td>
</tr>
<tr>
<td>5-FU—5-fluorouracil; 5-HT,—5-hydroxytryptamine; NK—natural killer; RA—receptor antagonist</td>
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Note. Based on information from the Oncology Nursing Society, 2014.
Case Study

A 71-year-old Caucasian male with a history of an unknown primary cancer by pathology, presumed to be either metastatic pancreatic adenocarcinoma or cholangiocarcinoma, was started on chemotherapy with oxaliplatin, irinotecan, 5-fluorouracil (5-FU), and leucovorin as part of the FOLFIRINOX regimen. Four days after receiving his first cycle of chemotherapy, he 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 IV antiemetics and fluids for supportive care. Five days after admission, he 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 he had worsening confusion and encephalopathy, despite his cultures being negative.

A repeat CT of the head and magnetic resonance imaging of the brain continued to show no abnormal findings. Neurology and psychiatry were consulted, and the patient was believed to have a non-localizing encephalopathy. The patient then became completely encephalopathic to the point where he was in a catatonic state. Multiple laboratory tests, including thyroid-stimulating hormone level and B₁₂, were all within normal limits. His ammonia level was the only elevated test. The patient was treated with lactulose for about four days with no improvement in mental status. After some discussion with his primary oncologist, the patient was tested for the dihydropyrimidine dehydrogenase enzyme activity. A blood sample was taken and sent to a laboratory in Utah. The patient was found to have a heterozygous gene mutation, IVS14+1G>A, the most common gene mutation. He was presumed to have 5-FU toxicity secondary to the inability to effectively metabolize 5-FU. A family meeting was initiated, and the patient’s 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 initiated, and the patient died a year later never having recovered from his encephalopathy.

screening method for DPD deficiency should be developed for better patient outcomes.

Advanced oncology nurse practitioners and oncology nurses must be vigilant in recognizing 5-FU toxicity to improve patient outcomes (Morrison et al., 1997). A comprehensive medical history should be done to determine if a patient or family history exists 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 be fully informed about the common and adverse side effects of 5-FU. In addition, nursing staff should be educated on the adverse side effects of severe 5-FU toxicity associated with DPD deficiency for prompt identification and medical intervention (Morrison et al., 1997). Nurses’ knowledge of pharmacogenetics in the treatment of patients receiving 5-FU could potentially influence a patient’s overall quality of life and prolong survival.

Supportive care is indicated and still continues to be the standard of care for patients with 5-FU toxicity. Patients and caregivers should immediately notify the treating healthcare provider of adverse side effects, and 5-FU administration should be discontinued. Adverse reactions should be treated at an early stage to prevent further medical complications for patients. The cost of genetic tests has rapidly declined over the last several years and is expected to continue to decline, with full genetic sequencing expected to cost less than $1,000 in the next five years (National Institutes of Health, 2013). The benefit of testing for DPYD mutations for a select group of patients is clear (Kristensen, Pedersen, Melsen, Ellehauge, & Mejer, 2010; Saif, 2013). When comparing the cost of care for an individual who develops severe 5-FU toxicity to the cost of pretesting for genetic variances associated with toxicity, testing may actually represent a more cost-effective and medically responsible option. Nurses who are involved in prechemotherapy education may wish to discuss the availability and limitations of these tests with patients considering treatment with a chemotherapy regimen containing 5-FU and advocate for their patients to be able to receive testing.

Implications for Nursing

High-quality patient assessment and education are imperative for the early identification and treatment of 5-FU–induced toxicity. Advanced oncology nurse practitioners and oncology nurses should thoroughly educate patients and their caregivers on the common and adverse side effects of 5-FU–based therapy and when it may be necessary to immediately contact their health-care provider. Patients should also be closely monitored and tested if they are thought to have the DPD enzyme deficiency. Any additional administration of 5-FU should be discontinued. Educational strategies to effectively teach nurses and practitioners about 5-FU toxicity associated with DPD deficiency should be developed because early recognition of 5-FU toxicity can improve patient outcomes.

Conclusion

Cost-effective screening tests for the DPD gene mutation and variants associated with 5-FU drug metabolism are greatly needed in the clinical setting to improve patient outcomes (Borrás et al., 2012). In the meantime, patients scheduled to receive 5-FU as part of their chemotherapy regimen should receive information about the possible consequences of severe 5-FU toxicity and the cost and availability of testing, which can help to determine their possible risk of developing severe toxicity. Early

Implications for Practice

- Educate patients and their caregivers on the common and adverse effects of 5-fluorouracil (5-FU)–based therapy, and educate them to report any abnormal changes in behavior.
- Monitor patients who are believed to have dihydropyrimidine dehydrogenase enzyme deficiency, and perform early testing if necessary.
- Detect early neurologic side effects by performing a thorough neurologic examination as part of a routine physical, and discontinue any further administration of 5-FU if any evidence of toxicity exists.
determination of DPD activity and DPYD mutation by radio assays 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). Unfortunately, because 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.

References


