Unanticipated Toxicity to Capecitabine

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A 63-year-old African American woman, L.L., was diagnosed with hormone-negative, HER2-negative, stage IIIa breast cancer 18 months ago. Following a left modified radical mastectomy with immediate reconstruction, L.L. was treated with dose-dense adriamycin-cyclophosphamide followed by paclitaxel. Follow-up visits were uneventful until a month ago, when she reported persistent right-upper quadrant abdominal pain.

Review of systems was negative except for fatigue that L.L. rated as 7 of 10 on a 10-point fatigue scale. Computed tomography scan showed three hepatic lesions, the largest measuring 1.7 cm. The remainder of the staging workup was negative for signs of metastatic disease. A needle biopsy of one of the liver lesions was positive for carcinoma consistent with the primary breast cancer. Capecitabine monotherapy at a dose of 1,000 mg BID for 14 days, followed by seven days of rest, was discussed with L.L. and her husband. Verbal and printed instructions were given on dosing, drug administration, and side effects, including symptoms that would require prompt contact with L.L.'s team.

The nurse practitioner called L.L. on day 4 and found that, other than mild nausea, L.L. was doing well. At 7 am on day 8, L.L.'s husband called to report that L.L. had been vomiting most of the night and had bloody diarrhea since 4 am. They were instructed to go immediately to emergency triage at the hospital. When L.L. presented to triage, she was hemodynamically unstable and was admitted to the intensive care unit (ICU) for monitoring. On admission, she was found to have grade 3 oral mucositis, grade 4 diarrhea, and grade 4 neutropenia. She remained unstable and in the ICU for 10 days, after which she was transferred to the oncology unit for another 18 days. Early in her four-week stay in the hospital, L.L. was tested for dihydropyrimidine dehydrogenase (DPD) and had partial deficiency. Capecitabine therapy had been interrupted on admission and was not resumed at discharge. L.L. was switched to gemcitabine, which she tolerated well.

What Is DPD Deficiency?

DPD deficiency is an autosomal recessive (inherited) metabolic disorder in which absent or significantly decreased activity of DPD, an enzyme involved in the metabolism of 80%–90% of the administered dose of 5-fluorouracil (5-FU), occurs. Components of 5-FU include uracil and thymine. DPD is the initial rate-limiting enzyme in pyrimidine catabolism (Fischel et al., 1995). The deficiency is a result of the allelic mutations within the *DPYD* gene (Etienne et al., 1994; Johnson & Diasio, 2001).

Severe toxicities following exposure to 5-FU or the 5-FU oral analog, capecitabine, are observed at higher rates in patients who are heterozygous (possessing two different forms of the gene) for the mutant *DPYD* allele, compared with patients who are homozygous (possessing two identical forms of the gene) for the wild-type, or unmutated, *DPYD* allele (Milano et al., 1999; Omura, 2003). In DPD deficiency, the pathway for metabolism of 5-FU does not function normally, resulting in accumulation of toxic compounds and prolonged exposure to 5-FU. Standard doses of 5-FU or capecitabine can result in severe mucositis, diarrhea, neutropenia, cerebellar ataxia, cerebellar dysfunction, and death. The mortality rate is almost 100% in patients with complete DPD deficiency who are exposed to 5-FU; fortunately, complete DPD deficiency is extremely rare.

Patients have a partial deficiency if the level of DPD activity falls below the 95th percentile and a complete deficiency if the level is below the 99th percentile or is undetectable (normal range 0.182–0.688 nmol/min/mg protein). About 3%–5% of patients with cancer are considered partially DPD deficient (Mattison, Soong, & Diasio, 2002).

What Are the Key Assessments for Severe Side Effects?

Because 5-FU side effects may appear in many body systems, a thorough review of systems is necessary, as is a review of concomitant medications, comorbidities, and laboratory findings. In a study of 23 patients with gastrointestinal cancer with severe 5-FU–related toxicities, grade 3 or 4 toxicities included mucositis (71%), diarrhea (43%), skin rash (43%), memory loss or altered mental status (43%), cytopenias (43%), nausea (29%), hypotension (14%), respiratory distress (14%), and acute renal failure (14%) (Saif, Syrigos, Mehra, Mattison, & Diasio, 2007).

The toxicity most often encountered in DPD-deficient patients who were exposed to 5-FU is grade 3 or 4 neutropenia. Other toxicities, such as mucositis, diarrhea, and neurologic dysfunction or multifocal inflammatory leukoencephalopathy also can occur (Franco & Greenberg, 2001; van Kuilenburg, Meinsma, Zoetekouw, & Van Gennip, 2002). In the capecitabine-treated population, rapid onset of grade 3 hand-foot syndrome may be caused by DPD deficiency (Saif, Syrigos, et al., 2007). If DPD deficiency is suspected, testing should be arranged at the earliest opportunity.

What Are the Risk Factors for DPD Deficiency?

Lu, Zhang, and Diasio (1993) observed slightly higher incidence in women, which was confirmed by Milano et al. (1999), although van Kuilenburg et al. (1999) were unable to confirm this gender effect. Schwab et al. (2008) reported on a multicenter prospective clinical trial assessing the predictive value of polymorphisms in *DPYD*, thymidylate synthase, and nongenetic factors for severe 5-FU–related toxicites. Genotype, female gender (two-fold higher risk than males), mode of 5-FU administration, and modulation by folic acid were identified as independent risk factors. In the Schwab et al. study, toxicity in women was independent of *DPYD* genotype. The greatest risk factor for DPD deficiency appears to be germline inheritance of the allelic mutations within the *DPYD* gene. A distinct pattern exists of DPD deficiency among

certain racial and ethnic groups, and the study of pharmacogenomic differences in DPD activity among different ethnic and racial groups continues to evolve (Saif, Syrigos, et al., 2007).

Retrospective data from a phase III trial of 5-FU in the adjuvant setting show a significant decrease in severe toxicity, such as diarrhea, nausea, and stomatitis in African Americans compared to Caucasians; however, an increase in overall leukopenia and anemia was noted in African Americans (McCollum, Catalano, & Haller, 2002). Differences in DPD activity between the two racial groups have been noted, with African Americans having a lower level of mean DPD activity and a three-fold higher incidence of DPD deficiency (Mattison et al., 2006). Overall, larger population studies including diverse ethnic groups are required to fully characterize the incidence of DPD deficiency and *DPYD* mutations.

How Common Is DPD Deficiency?

The pharmacogenetic syndrome of DPD deficiency occurs in 3%–5% of the general population. Among patients with severe 5-FU–related toxicities, 30%–57% of toxicities are attributed to DPD deficiency (Morel et al. 2006; van Kuilenburg et al., 2002). An estimated two million patients receive 5-FU–based therapy worldwide each year (Ezzeldin & Diasio, 2004). If the incidence of DPD deficiency in the cancer population is about 3%, this equates to potentially severe side effects and hospitalization in about 60,000 patients annually.

How Is DPD Diagnosed?

Advances in diagnostic testing have made testing for DPD activity and *DPYD* genetic mutations available to hospitals, community oncology practices, and cancer centers. An enzymatic radioassay to determine the activity of DPD, and a polymerase chain reaction (PCR)-based assay to detect a mutation in the *DPYD* gene associated with increased DPD activity are the principal laboratory tests for identifying patients with DPD deficiency. The most common enzymatic radioassay is a leukocyte or fibroblast assay. Decreased leukocyte DPD activity parallels the decreased activity in hepatic 5-FU catabolism (van Kuilenburg et al., 1997); however, a large range of DPD activity has been detected when these types of cells are used, therefore hampering accurate diagnosis (van Kuilenburg, van Lenthe, Tromp, Veltman, & Van Gennip, 2000).

The semi-automated peripheral blood mononuclear cell DPD radioassay is performed on a peripheral whole blood draw and uses radioassay to measure DPD blood levels. The genotype of the *DPYD* gene is analyzed using a PCR assay to test for the most common *DPYD* gene mutation, IVS14 + 1 G > A, also known as DPYD*2A, which accounts for 52% of all *DPYD* mutations (Saif, Ezzeldin, Vance, Sellers, & Diasio, 2007; van Kuilenburg et al., 1999). A rapid 2–^{13}C uracil breath test uses post–5-FU dose administration breath samples collected into 100 ml breath bags. Two breath tests are currently in clinical trials: UraBT and 2–^{13}C fluorouracil breast test (Mattison, Ezzeldin, et al., 2004; Mattison, Fourie, et al., 2004). Screening patients for DPD deficiency prior to administration of 5-FU or capecitabine using a rapid uracil breath test could lower the incidence of severe toxicity by proactively identifying at-risk patients. Additional studies are needed to validate this technique (Saif, Syrigos, et al., 2007). Commercially available DPD tests are found in Table 1.

How Are Severe 5-Fluorouracil Side Effects Managed?

Patients with severe side effects to 5-FU–based therapies require emergent evaluation and treatment. Patients on capecitabine therapy must be instructed to interrupt treatment until advised to resume (Roche Laboratories, 2006). Assessment of symptoms should alert the nurse to suspect DPD deficiency because of the rapid onset, duration, and severity of toxicities, which are out of the expected range of known side effects to 5-FU–based therapy. Almost all patients with 5-FU toxicity related to DPD deficiency are hemodynamically and physically unstable; emergent admission to an ICU unit or an oncology unit with cardiac monitoring is strongly recommended.

Table 1. Dihydropyrimidine Dehydrogenase (DPD) Deficiency Testing

Test Name	Manufacturer	Type of Test Specimen	Comments
DPD Enzyme Deficiency Test for Fluorouracil	Genelex Seattle, WA +1-800-523-3080 www.healthanddna.com	Whole blood or buccal swab collection	Can be self-ordered by patient except in Maryland and California, where physician order is required Not available in New York PCR Five business day report
DPD 5FU GenotypR™	Specialty Laboratories Valencia, CA +1-800-421-7110 www.specialtylabs.com	Whole blood	PCR Next-day report
DPD 5-Fluorouracil Toxicity	Laboratory Corporation of America San Diego, CA +1-800-859-6046 www.labcorp.com	Whole blood or buccal swab collection	Collection sites throughout the United States Check Web site for locations. PCR
TheraGuide 5FU™	Myriad Genetic Laboratories, Inc. Salt Lake City, UT +1-800-469-7423 www.myriadtests.com	Whole blood Test kit can be ordered by phone or online.	Full gene sequencing Seven-day report

PCR—polymerase chain reaction

These patients cannot be safely managed at home because uncontrolled diarrhea and mucositis can lead to sequelae such as dehydration, multi-organ system failure, and death. Neutropenia may result in gram-negative infection and sepsis, particularly when accompanied by mucositis or diarrhea. Patients with neurologic symptoms should have a full evaluation by a neurologist or a neuro-oncologist to rule out leukoencephalopathy or brain metastases. Management of specific 5-FU–related side effects is beyond the scope of this case discussion. Evidence-based guidelines for diarrhea management are available from the Oncology Nursing Society ([ONS], 2008). Guidelines for infection are available from the National Comprehensive Cancer Network (2008) and ONS (2005). Oncology nurses should be prepared to provide a full report of the patient's condition to emergency triage or the receiving unit, including chemotherapy history, condition at last clinic visit, medication and allergy histories, and contact information. If the oncology nurse instructed the patient to proceed to emergency triage, the attending oncologist should be notified.

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References

Etienne, M.C., Lagrange, J.L., Dassonville, O., Fleming, R., Thyss, A., Renee, N., et al. (1994). Population study of dihydropyrimidine dehydrogenase in cancer patients. *Journal of Clinical Oncology, 12*(11), 2248–2253.

Ezzeldin, H., & Diasio, R. (2004). Dihydropyrimidine dehydrogenase deficiency, a pharmacogenetic syndrome associated with potentially life-threatening toxicity following 5-fluorouricil administration. *Clinical Colorectal Cancer, 4*(3), 181–189.

Fischel, J.L., Etienne, M.C., Spector, T., Formento, P., Renee, N., & Milano, G. (1995). Dihydropyrimidine dehydrogenase: A tumoral target for fluorouracil modulation. *Clinical Cancer Research, 1*(9), 991–996.

Franco, D.A., & Greenberg, H.S. (2001). 5-FU multifocal inflammatory leukoencephalopathy and dihydropyrimidine dehydrogenase deficiency. *Neurology, 56*(1), 110–112.

Johnson, M.R., & Diasio, R.B. (2001). Importance of dihydropyrimidine dehydrogenase (DPD) deficiency in patients exhibiting toxicity following treatment with 5-fluorouracil. *Advances in Enzyme Regulation, 41*(1), 151–157.

Lu, Z., Zhang, R., & Diasio, R.B. (1993). Dihydropyrimidine dehydrogenase activity in human peripheral blood mononuclear cells and liver: Population characteristics, newly identified deficient patients, and clinical implication in 5-fluorouracil chemotherapy. *Cancer Research, 53*(22), 5433–5438.

Mattison, L.K., Ezzeldin, H., Carpenter, M., Modak, A., Johnson, M.R., & Diasio, R.B. (2004). Rapid identification of dihydropyrimidine dehydrogenase deficiency by using a novel 2–^{13}C-uracil breath test. *Clinical Cancer Research, 10*(8), 2652–2658.

Mattison, L.K., Fourie, J., Desmond, R.A., Modak, A., Saif, M.W., & Diasio, R.B. (2006). Increased prevalence of dihydropyrimidine dehydrogenase deficiency in African Americans compared with Caucasians. *Clinical Cancer Research, 12*(18), 5491–5495.

Mattison, L.K., Fourie, J., Hirao, Y., Koga, T., Desmond, R.A., King, J.R., et al. (2004). The uracil breast test in the assessment of dihydropyrimidine dehydrogenase activity: Pharmacokinetic relations between expired $^{13}CO_2$ and plasma [2-^{13}C] dihydrouracil. *Clinical Cancer Research, 12*(2), 549–555.

Mattison, L.K., Soong, R., & Diasio, R.B. (2002). Implications of dihydropyrimidine dehydrogenase on 5-fluorouracil pharmacogenetics and pharmacogenomics. *Pharmacogenomics, 3*(4), 485–492.

McCollum, A.D., Catalano, P., & Haller, D. (2002). Outcomes and toxicity in African American and Caucasian patients in a randomized adjuvant chemotherapy trial for colon cancer. *Journal of the National Cancer Institute, 94*(15), 1160–1167.

Milano, G., Etienne, M.C., Pierrefite, V., Barberi-Heyob, M., Deporte-Fety, R., & Renee, N. (1999). Dihydropyrimidine dehydrogenase deficiency and fluorouracil-related toxicity. *British Journal of Cancer, 79*(3/4), 627–630.

Morel, A., Boisdron-Celle, M., Fey, L., Soulie, S., Craipeau, M.C., Traore, S., et al. (2006). Clinical relevance of different dihydropyrimidine dehydrogenase gene single nucleotide polymorphisms on 5-fluorouracil tolerance. *Molecular Cancer Therapeutics, 5*(11), 2895–2904.

National Comprehensive Cancer Network. (2008). *NCCN Clinical Guidelines in Oncology™: Prevention and treatment of cancer-related infections.* Retrieved November 17, 2008, from http://nccn.org/professionals/physician_gls/PDF/infections.pdf

Omura, K. (2003). Clinical implications of dihydropyrimidine (DPD) activity in 5FU-based chemotherapy: Mutations in the DPD gene and DPD inhibitory fluoropyrimidines. *International Journal of Clinical Oncology, 8*(3), 132–138.

Oncology Nursing Society. (2005). *Prevention of infection PEP® resource card.* Retrieved November 17, 2008, from http://ons.org/outcomes/volume1/prevention/pdf/InfectionPEPCard.pdf

Oncology Nursing Society. (2008). *Diarrhea ONS PEP® resource card.* Retrieved November 12, 2008, from http://www.ons.org/outcomes/volume4/diarrhea/pdf/ShortCard_Diarrhea.pdf

Roche Laboratories. (2006). *Xeloda* [prescribing information]. Retrieved November 3, 2008, from http://www.rocheusa.com/products/xeloda/pi.pdf

Saif, M.W., Ezzeldin, H., Vance, K., Sellers, S., & Diasio, R.B. (2007). *DPYD**2A mutation: The most common mutation associated with DPD deficiency. *Cancer Chemotherapy Pharmacology, 60*(4), 503–507.

Saif, M.W., Syrigos, K., Mehra, R., Mattison, L.K., & Diasio, R.B. (2007). Dihydropyrimidine dehydrogenase deficiency (DPD) in GI malignancies: Experience of four years. *Pakistan Journal of Medical of Sciences Quarterly, 23*(6), 832–839.

Schwab, M., Zanger, U.M., Marx, C., Schaeffeler, E., Klein, K., Dippon, J., et al. (2008). Role of genetic and nongenetic factors for fluorouracil treatment-related severe toxicity: A prospective clinical trial by the German 5-FU toxicity study group. *Journal of Clinical Oncology, 26*(13), 2131–2138.

van Kuilenburg, A.B., Meinsma, R., Zoetekouw, L. & Van Gennip, A.H. (2002). Increased risk of grade IV neutropenia after administration of 5-fluorouracil due to a dihydropyrimidine dehydrogenase deficiency: High prevalence of the IVS14+1g > a mutation. *International Journal of Cancer, 101*(3), 253–258.

van Kuilenburg, A.B., van Lenthe, H., Tromp, A., Veltman, P., & Van Gennip, A.H. (2000). Pitfalls in the diagnosis of patients with a partial dihydropyrimidine dehydrogenase deficiency. *Clinical Chemistry, 46*(1), 9–17.

van Kuilenburg, A.B., Vreken, P., Abeling, N., Bakker, H.D., Meinsma, R., Van Lenthe, H., et al. (1999). Genotype and phenotype in patients with dihydropyrimidine dehydrogenase deficiency. *Human Genetics, 104*(1), 1–9.

van Kuilenburg, A.B., Vreken, P., Beex, L., Meinsma, R., van Lenthe, H., De Abreu, R.A., et al. (1997). Heterozygosity for a point mutation in an invariant splice donor site of dihydropyrimidine dehydrogenase and severe 5-fluorouracil related toxicity. *European Journal of Cancer, 33*(13), 2258–2264.

Clinical Highlights: Dihydropyrimidine Dehydrogenase Deficiency

Definition

Dihydropyrimidine dehydrogenase (DPD) deficiency is an autosomal recessive metabolic disorder in which DPD activity is absent or significantly decreased. DPD is an enzyme involved in the metabolism of uracil and thymine, components of 5-fluorouracil (5-FU) (Etienne et al., 1994). Patients with this condition may develop life-threatening toxicity following exposure to 5-FU (van Kuilenburg, 2006).

Pathophysiology

In humans, 80%–90% of an administered dose of 5-FU is degraded by DPD, which is the initial rate-limiting enzyme in pyrimidine catabolism (Fischel et al., 1995). Patients have a partial deficiency if the level of DPD activity falls below the 95th percentile and a complete deficiency if the level is below the 99th percentile or is undetectable (normal range 0.182–0.688 nmol/min/mg protein) (Mattison, Soong, & Diasio, 2002). DPD deficiency is a result of the allelic mutations within the *DPYD* gene (Etienne et al., 1994; Johnson & Diasio, 2001). Severe toxicities following exposure to 5-FU or the 5-FU oral analog, capecitabine, are observed at higher rates in patients who are heterozygous (possessing two different forms of the gene) for the mutant *DPYD* allele, compared with patients who were homozygous (possessing two identical forms of the gene) for the wild-type, or unmutated, *DPYD* allele (Milano et al., 1999; Omura, 2003). In DPD deficiency, the pathway for metabolism of 5-FU does not function normally, resulting in accumulation of toxic compounds and prolonged exposure to 5-FU.

Risk Factors

Risk factors for DPD deficiency include inheritance of a *DPYD* gene mutation (Etienne et al., 1994; Johnson & Diasio, 2001) and African American race (Mattison et al., 2006).

Prevention

No specific interventions exist to prevent DPD deficiency because the condition has no recognizable phenotype. DPD deficiency testing is the only viable screening method. Awareness of high-risk patient categories should alert the nurse to discuss DPD deficiency testing with the oncologist prior to chemotherapy.

Clinical Findings and Diagnostic Workup

5-FU–related toxicities may appear in several body systems, so a full review of systems is essential before proceeding with diagnostic workup. In addition to standard laboratory tests (complete blood count, complete metabolic panel, hepatic enzymes), stool workup should be evaluated. An enzymatic radioassay to determine the activity of DPD and a polymerase chain reaction-based assay to detect a mutation in the *DPYD* gene associated with increased DPD activity are the principal laboratory tests for identifying patients with DPD deficiency. The most common enzymatic radioassay is a leukocyte or fibroblast assay. Decreased leukocyte DPD activity parallels the decreased activity in hepatic 5-FU catabolism (van Kuilenburg et al., 1997); however, a large range of DPD activity has been detected when these types of cells are used, therefore hampering accurate diagnosis (van Kuilenburg, van Lenthe, Tromp, Veltman, & Van Gennip, 2000).

Differential Diagnoses

Differential diagnoses for severe gastrointestinal symptoms include small bowel enteritis, *Clostridium difficile*, ulcerative colitis, and colitis secondary to infection with enteric pathogens such as *Escherichia coli*, salmonella, or shigella. Brain metastases, leukoencephalopathy, or cerebrovascular accident should be ruled out before testing for DPD deficiency.

Treatment and Guidelines

No treatment exists to correct the genetic mutation that results in DPD deficiency. Treatment for severe 5-FU–related toxicity involves prompt and expert management of the specific toxicities.

Nursing Implications

DPD testing is readily available to identify safe and effective treatments. Patient safety can be improved by careful patient and caregiver education with respect to early reporting of side effects and a clear understanding of which side effects can be managed at home before contacting the oncology nurse. If DPD deficiency is confirmed, patients can be treated with alternate regimens containing nonfluoropyrimidine agents with activity in breast cancer, such as gemcitabine, navelbine, ixabepilone, or a taxane.

References

Etienne, M.C., Lagrange, J.L., Dassonville, O., Fleming, R., Thyss, A., Renee, N., et al. (1994). Population study of dihydropyrimidine dehydrogenase in cancer patients. *Journal of Clinical Oncology, 12*(11), 2248–2253.

Fischel, J.L., Etienne, M.C., Spector, T., Formento, P., Renee, N., & Milano, G. (1995). Dihydropyrimidine dehydrogenase: A tumoral target for fluorouracil modulation. *Clinical Cancer Research, 1*(9), 991–996.

Johnson, M.R., & Diasio, R.B. (2001). Importance of dihydropyrimidine dehydrogenase (DPD) deficiency in patients exhibiting toxicity following treatment with 5-fluorouracil. *Advances in Enzyme Regulation, 41*(1), 151–157.

Mattison, L.K., Soong, R., & Diasio, R.B. (2002). Implications of dihydropyrimidine dehydrogenase on 5-fluorouracil pharmacogenetics and pharmacogenomics. *Pharmacogenomics, 3*(4), 485–492.

Milano, G., Etienne, M.C., Pierrefite, V., Barberi-Heyob, M., Deporte-Fety, R., & Renee, N. (1999). Dihydropyrimidine dehydrogenase deficiency. *British Journal of Cancer, 79*(3/4), 627–630.

Omura, K. (2003). Clinical implications of dihydropyrimidine (DPD) activity in 5FU-based chemotherapy: Mutations in the DPD gene and DPD inhibitory fluoropyrimidines. *International Journal of Clinical Oncology, 8*(3), 132–138.

van Kuilenburg, A.B. (2006). Screening for dihydropyrimidine dehydrogenase deficiency: To do or not to do, that's the question. *Cancer Investigation, 24*(2), 215–217.

van Kuilenburg, A.B., van Lenthe, H., Tromp, A., Veltman, P., & Van Gennip, A.H. (2000). Pitfalls in the diagnosis of patients with a partial dihydropyrimidine dehydrogenase deficiency. *Clinical Chemistry, 46*(1), 9–17.

van Kuilenburg, A.B., Vreken, P., Beex, L., Meinsma, R., van Lenthe, H., De Abreu, R.A., et al. (1997). Heterozygosity for a point mutation in an invariant splice donor site of dihydropyrimidine dehydrogenase and severe 5-fluorouracil related toxicity. *European Journal of Cancer, 33*(13), 2258–2264.