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, or 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 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 toxicities. 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 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%), hypertension (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 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%), hypertension (14%), respiratory distress (14%), and acute renal failure (14%) (Saif, Syrigos, Mehra, Mattison, & Diasio, 2007).

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