

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

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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.

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Key words: chemotherapy; quality of life; supportive therapies

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

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, Mat-

tison, & 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, 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 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