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.