DPD Mechanism of Action

5-Fluorouracil and capecitabine are two of the most frequently prescribed chemotherapeutic drugs for patients with cancers of the gastrointestinal tract, breast, and head and neck. In most patients, nearly 85% of 5-FU administered is metabolized by dihydropyrimidine dehydrogenase (DPD), rendering about 15% of the dose active.

Normal
When 5-FU enters the system, the majority of the drug is rendered inactive when it interacts with the DPD enzyme. The remaining active 5-FU represents an effective dose. The 5-FU binds with the TS enzyme restricting DNA synthesis and cell division primarily in cancerous cells.

However, individuals with complete or partial DPD deficiency have a strongly reduced capacity to metabolize 5-FU and therefore experience severe, and sometimes life-threatening, toxic effects from the increased levels of active drug.

DPD Deficiency
In the presence of certain variations in \(DPYD\), lower amounts of DPD enzyme are available to adequately inactivate the normal 5-FU dose. This results in higher levels of active drug in the body prohibiting DNA synthesis and leading to adverse events.

Testing for DPD deficiency, and thus identifying patients with an increased risk for toxicity to 5-FU and capecitabine, lends itself to the unique opportunity to prescreen patients and to minimize, or even eliminate, these toxicities. Furthermore, DPD deficiency is now recognized formally as a contraindication for the use of capecitabine and other fluoropyrimidines, lending additional support to the necessity of developing a prescreening program for a DPD deficiency.\(^1\,^2\,^3\)

**Bottom Line:**
“From an ethical point of view, the screening of patients for the presence of DPD deficiency prior to the start of treatment with fluoropyrimidines is warranted.” Full sequence analysis of the \(DPYD\) gene is the most comprehensive method available for identifying patients with DPD deficiency.

\(^1\) Van Kuilenburg. Screening for Dihydropyrimidine Dehydrogenase Deficiency: To Do or Not To Do, That’s The Question. Cancer Investigation. 2006;24:215-17.
\(^2\) http://www.fda.gov/medwatch/SAFETY/2003/mar03.htm#xeloda.
\(^3\) http://www.merck.com/mmpe/lexicomp/fluorouracil.html.