DPYD genetic testing allows individualised dosing of fluoropyrimidines, resulting in less toxicity without loss of effectiveness.

The fluoropyrimidines, 5-fluorouracil (5-FU) and capecitabine, are widely used in the treatment of solid tumours, including colorectal cancer, breast cancer and cancers of the upper gastrointestinal tract. Approximately 30% of patients experience treatment-related toxicity, with the complications being fatal in up to 1% of patients. Severe systemic reactions can also occur following topical application for the treatment of skin lesions.¹

Recent studies have documented that individualised dosing based on DPYD gene testing can reduce toxicity while retaining the effectiveness of these medications. DPYD encodes a key enzyme involved in the metabolism of these medications. These results are in keeping with international guidelines on fluoropyrimidine dosing.

**DPYD testing results in lower toxicity with fluoropyrimidines**

In 2018, Henricks et al. described a multi-centre prospective trial of 1,107 consecutive patients being prescribed 5-FU or capecitabine, either as single agent or in combination.² Eighty-five patients (7%) had one of the pre-specified variants in the DPYD gene which compromise fluoropyrimidine metabolism. These patients had dose reductions in keeping with extant dosing guidelines.

Overall, the rate of Grade 3 toxicity was higher among those with, rather than without, these variants. However, when compared with a historical cohort who had had genetic testing but no dose reduction, the dose reduction significantly reduced the relative rate (RR) of Grade 3 toxicity in those with the DPYD*2A or c.2846A>T variants (p<0.05, Figure 1). A patient with the c.2846A>T variant died after inadvertently receiving the full dose of capecitabine. The benefit of reduced dosing was evident for a third variant but did not achieve significance.

**Individualised DPYD dosing does not compromise effectiveness**

In a related study, the authors described a cohort of 40 patients with the DPYD*2A variant who were treated with a reduced dose of fluoropyrimidine.³ Their survival was compared with matched controls with no DPYD variants given full-dose therapy.

There was no difference in overall survival or progression-free survival over the seven years of follow-up. The toxicity among those with the variant and the low-dose regime was the same as among those with the normal gene and dosing.

**International dosing guidelines for fluoropyrimidines recommend DPYD testing**

These findings are in keeping with recommendations from the Clinical Pharmacogenomic Implementation Committee (CPIC)⁴ that DPYD genetic testing be done prior to initiating therapy with fluoropyrimidines, and that doses be adjusted according to the predicted enzyme activity.

**DPYD testing is available nationally through Sonic Genetics. The test detects the following variants: c.1905+1G>A (DPYD*2A), c.1679T>G, c.2846A>T, and c.1129–5923C>G. The report provides explicit dosing recommendations.**

*Correct at time of print. Please refer to www.sonicgenetics.com.au/pricing for current price

**References**


*Figure 1. The relative risk of toxicity in those with versus without the specified variant when treated with full or individualised dose.*