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Genetic testing to predict 5-FU/capecitabine toxicity

Bulletin for Prescribers | August 2019

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.

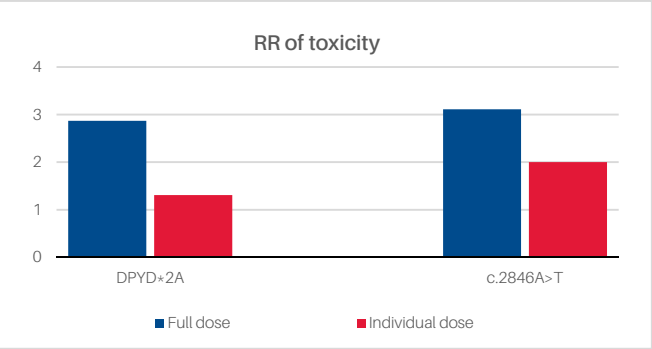

Figure 1. The relative risk of toxicity in those with *versus* without the specified variant when treated with full or individualised dose.

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.*

The cost is $200 and a Medicare rebate is not available. The turnaround time is up to 10 business days, and results can be accessed electronically via Sonic Dx, by fax or by phone.*

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

References

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2. Henricks L, Lunenburg CATC, de Man FM, et al. DPYD genotype-guided dose individualisation of fluoropyrimidine therapy in patients with cancer: a prospective safety analysis. *Lancet Oncol.* 2018;19(11):1459-1467
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