An evaluation of the clinical utility of a panel of variants in DPYD and ENOSF1 for predicting common capecitabine related toxicities

Claire Palles 1, Susan Fotheringham 2, Laura Chegwidden 1, Marie Lucas 3, Guy Mozolowski 2, Ian Tomlinson 1, David Kerr 2, 4


Introduction

5-Fluorouracil (5-FU) based adjuvant chemotherapy, including 5-FU oral prodrug capecitabine, is extremely effective in increasing survival of Stage III colorectal cancer (CRC) patients and patients with resectable gastric or breast cancer. Its use is however limited by the concomitant toxicities that arise in some patients. ~50% of patients experience dose limiting toxicity when treated with capecitabine as a single agent and this percentage increases when given in combination e.g. with oxaliplatin. We have tested the diagnostic accuracy of a panel of toxicity associated/DPYD deficiency alleles at predicting an individual’s risk of capecitabine-related toxicity in 888 patients from the QUASAR2 trial.

Methods

Table 1: Recommended dosing of fluoropyrimidines based on genotype or DPYD activity (adapted from Cauld et al, 2013)

<table>
<thead>
<tr>
<th>Phenotype (genotype)</th>
<th>Implications for treatment</th>
<th>Dosing recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homozygous for wild-type allele, or normal, high DPYD activity</td>
<td>Normal DPYD activity “normal” risk for toxicity</td>
<td>Use label-recommended dosage and administration</td>
</tr>
<tr>
<td>Heterozygous, or intermediate activity</td>
<td>Decreased DPYD activity, increased risk for severe or even fatal drug toxicity</td>
<td>Start with at least a 50% dose reduction, followed by titration of dose based on toxicity or pharmacokinetic test</td>
</tr>
<tr>
<td>Homozygous, or deficient activity</td>
<td>Complete DPYD deficiency increased risk for severe or even fatal drug toxicity</td>
<td>Select alternative drug</td>
</tr>
</tbody>
</table>

Criteria for including a genetic marker in the toxicity panel:

- **Low function/no function alleles** - Identified in DPYD deficiency patients (minor allele frequency (MAF) <1%). Three were also associated with toxicity at P <0.05.
- **Common polymorphisms associated with global capecitabine-related toxicity** with an odds ratio >1.5 at pathway level significance and with an individual toxicity at genome-wide significance.

DPYD genotype based dosing guidelines published in 2013 (Table 1) were incorporated in a simple genotype guided risk classification system resulting in critical risk, high risk, standard risk and standard risk with high risk of hand foot syndrome (HFS) classifications.

Clinical utility of the panel was tested by genotyping the markers in 888 participants of the QUASAR2 trial (Kerr et al, 2016) for whom DNA and CTCAE graded toxicity data were available. Updated guidelines also recommend dose reductions based on DPYD haplotype c.1236G>A/HapB3. We have evaluated the impact of including this variant.

Results

17 DPYD low-function/no-function alleles, 1 common (MAF>1%) polymorphism mapping to DPYD and one common polymorphism mapping to ENOSF1 were selected for inclusion in the panel.

The following adverse event outcomes were analysed to determine the clinical utility of the panel at predicting toxicity: Toxicity associated death, Haematological toxicities (grade 0,1,2 vs 3,4), Global toxicity (cases coded as having one or more graded 3/4 event of diarrhoea, neutropenia, thrombocytopenia, vomiting, stomatitis/mucositis, hand foot syndrome (HFS)).

The test has high sensitivity and specificity to accurately predict risk of death or grade 4 haematological toxicities (100% sensitivity, 98% specificity, negative predictive value (NPV) 1.0, positive predictive value (PPV) 0.1 (death); 75% sensitivity, 98% specificity , NPV 1, PPV 0.14 (haematological toxicities). The ability of the test to predict risk of other toxicities is low (Figure 1, Global Toxicity).

The two deaths during QUASAR2 which were attributable to capecitabine administration occurred in patients who would have been highlighted by the test as high risk and a 50% reduction in starting dose would have been recommended. Common markers associated with HFS at genome wide significance were included in the panel. The sensitivity and specificity of the panel to accurately predict risk of HFS is only moderate (83% sensitivity, 31% specificity, NPV 0.87, PPV 0.25) but explanation by an oncologist of ways to mitigate the impact of this side effect on quality of life may enable participants to continue with treatment for longer. Inclusion of HapB3 in the panel was not supported as evidenced by reduced area under the curve and reduced sensitivity/specificity (data not shown).

Conclusions

A panel of no-function/low-function DPYD alleles has clinical utility for the prediction of the most serious capecitabine related adverse events. Inclusion of two HFS associated markers may assist clinicians and patients in the management of this side effect. A clinical utility study is under way to determine the impact of testing for this panel of variants on patient treatment decisions.

References: