UK Chemotherapy Board

Personalised Medicine Approach For Fluoropyrimidine-based Therapies

This document has been endorsed by the UK chemotherapy board member organisations.

It has been written by Dr Paul Ross, Consultant Medical Oncologist, Guys and St Thomas NHS Foundation Trust and Dr Tony Marinaki, Clinical Scientist, Purine Research Laboratory, Viapath.

It is recommended that all Hospital trusts and organisations should adopt this guidance for local use.

Objective:
To provide clinical staff with guidance as to which patients should receive a DPD test and then subsequently to provide advice to clinical staff on the outcome of that test.

Scope:

This guidance covers all necessary tumour groups and is relevant to all clinical staff involved with the management of patients within these tumour groups.

Responsibilities:

Clinical staff member	Responsibility
SACT lead and Lead nurse or Matron for SACT.	To ensure that this procedure has been highlighted and made available to all members of staff.
Consultant	Ensuring their team are aware that each patient due to receive a fluoropyrimidine has a DPD test prior to starting treatment. This includes explaining the test to the patient, ordering the test and then following up with the test outcome.
Specialist Registrar/other Prescriber	Explaining the test to the patient, ordering the test and then following up with the test outcome.
Pharmacist	During clinical verification of a prescription containing a fluoropyrimidine, ensuring a DPD test is taken prior to cycle 1. If this has not been done, contacting the consultant for advice on how to proceed.
Chemotherapy nurse	Prior to administration of a fluoropyrimidine for the first cycle, ensuring a DPD test has been done and liaising with pharmacy and the medical team if a DPD test has not been taken or the result is unavailable.

Abbreviations:

5FU - Fluorouracil

DPD/DYPD – dihydropyridimine dehydrogesase

EMA – European Medicines Agency

FDA – Food and Drug Administration

FEC – Fluorouracil, Epirubicin, Cisplatin

Background

Fluoropyrimidines (5-fluorouracil, capecitabine and the oral prodrug tegafur) are used as the basis of adjuvant and palliative treatment for colorectal, oesophago-gastric, breast and head and neck cancers. In addition, there is increasing use of the same group of drugs in pancreatic cancer and hepato-biliary malignancies. Treatment with fluoropyrimidines is generally well tolerated. However, severe adverse drug reactions have been recognised to occur in 5 – 10% of the treated population.[1, 2, 3] A significant proportion of adverse drug reactions are likely to be the result of inter-individual genetic variation.

The metabolic pathways by which 5-fluorouracil (5FU) is converted to active nucleotide analogues is well described.[4] Dihydropyrimidine dehydrogenase inactivates 80-90% of 5FU (DPD, encoded by the *DPYD* gene) into 5,6-dihydro-fluorouracil[5] . DPD deficiency is found in 3 – 6% of the population and has been associated with severe toxicity (diarrhoea, neutropenia, mucositis).[6, 7, 8] Polymorphisms in *DPYD* is the best recognised cause of primary deficiency of DPD associated with severe toxicity. The most clinically relevant polymorphism is DPYD*2A (IVS14+1G>A, c. 1905+ 1G>A, or rs3918290) and c.2846A>T (D949V or rs67376798).[9, 10] A meta-analysis has demonstrated that additional DPYD variants c. 1679T>G and c.1236G>A/HapB3DPYD are clinically relevant predictors of fluoropyrimidine toxicity.[11]

On 30th April 2020 the European Medicines Agency recommended patients should be tested for the lack of DPD before starting cancer treatment with fluorouracil given by injection or infusion (drip) or with the related medicines, capecitabine and tegafur.[12] Scientific groups such as the Clinical Pharmacogenetics Implementation Consortium and the Dutch Pharmacogenetics Working Group provide updated gene and drug clinical practice guidelines. This group currently recommend a 25 – 50% reduction in dose of 5FU or capecitabine for the first cycles followed by dose titration guided by toxicity in subsequent cycles for those patients with DPD deficiency.

Deenen and colleagues have now provided evidence that supports the implementation of genotypic testing for *DPYD* variants before the administration of the 5FU prodrug, capecitabine.[13] In this study participants heterozygous for the DPYD *2A variant were treated with a reduced dose of capecitabine whereas patients without the variant were treated with the standard dose of capecitabine. Although strict dosage rules were not implemented, the initial dose administered to those heterozygous for the variant was 50% of the standard dose. Further dose adjustments were made by the treating physician based on toxicity and experience. Overall, of the 18 participants with DPYD*2A variant included in the study only 5 (28%) experienced ≥ grade 3 toxicity. This rate is lower than the 70 – 90% of grade ≥3 toxicity previously reported in this population.[13, 14] Nonetheless, this report is limited by the limited efficacy data included and absence of long-term follow-up. Lunenburg and colleagues have shown that DPYD testing and pharmacogenomically directed dosing can be implemented in practice.[15] This study used a model where identified DPD alleles are assigned a score based on the impact on DPD activity. The initial dose administered is based on the total score.[16]

Guidance

All patients being considered for fluoropyrimidine (i.e. capecitabine, 5-fluorouracil, tegafur) based therapy should undergo pre-treatment pharmacogenomic screening for the four variants of DPYD associated with severe toxicity:

- DPYD*2A (IVS14+1G>A, c. 1905+ 1G>A, or rs3918290)
- c.2846A>T, p.D949V (rs67376798)
- DYPD*13, c.1679T>G, p.I560S (rs55886062))
- c.1236G>A/HapB3DPYD (rs56038477)
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All patients due to receive fluoropyrimidine based therapy, should have a DPD test prior to starting treatment.

Any patient who has not had a DPD test should be discussed with the consultant prior to going ahead. In exceptional circumstances where an agreement is made from the consultant that the patient can go ahead without a DPD test, the consultant or pharmacist must document clearly on the chemotherapy prescribing system and in the patient's medical record.

Ordering a DPD test

Each organisation should ensure there is a clear SOP for requesting a DPD test. Details of the local testing facility should be available and working with the laboratory a turnaround time of <5 days should be aimed for.

Interpreting the result

Patients identified as having one or more copies of these variants should be considered for dose modification of fluoropyrimidines or alternative therapy that is not a substrate for DPD as suggested in Table 1 and Table 2 below. Dose levels can cautiously be increased subsequently as determined by toxicity levels. There is little data around specific increment levels to increase by, but a recommendation would be to increase by 12.5% per cycle assuming no toxicity. It is recommended that there are at most 2 stepwise increments.
Where a patient has had significant toxicities but the DPD test has shown none of the variants to be present, a further test can be conducted to test the presence of rarer variants.

Table 1. *DPYD* heterozygous genotype and recommended dose reduction

allele	% DPD activity associated with a heterozygous genotype	Recommended dose adjustment for a heterozygous genotype
c.1905+ 1G>A (IVS14+1G>A)	50	50% dose reduction or alternative therapy*. If tolerant after the first cycle, dose increment to a dose of 75% of the target dose over subsequent cycles.
c.1679T>G (p.I560S)	50	50% dose reduction or alternative therapy*. If tolerant after the first cycle, dose increment to a dose of 75% of the target dose over subsequent cycles.
c.2846A>T (p.D949V)	50-75	50% dose reduction. If tolerant after the first cycle, dose increment to a dose of 75% of the target dose over subsequent cycles. If no toxicity is observed at a dose of 75%, a further increment to a maximum of 85% may be possible, but caution is advised.
c.1236G>A/HapB3DPYD	50-75	50% dose reduction. If tolerant after the first cycle, dose increment to a dose of 75% of the target dose over subsequent cycles. If no toxicity is observed at a dose of 75%, a further increment to a maximum of 85% may be possible, but caution is advised.

* The choice of dose reduced fluoropyrimdine or alternate therapy will be informed by the tumour type, clinical indication and predicted severity of enzyme deficiency based on DPYD genotype. When alternative therapy is recommended the suggested alternate therapy (raltitrexed or trifluridine/tipiracil) is appropriate where the treating oncologist considers the

inclusion of an anti-metabolite the optimal therapeutic option. It is beyond the scope of this guideline to state the appropriate decision for each indication.

For compound heterozygous or homozygous genotypes, the effect of the variant alleles on dose reduction is additive.

Table 2. Recommended dose reduction for homozygous and compound heterozygous variant *DPYD* genotypes.

Homozygous and compound heterozygous genotypes	% DPD activity	Recommended dose adjustment
c.1236G>A/HapB3/c.1905+1G>A compound heterozygous or c.1905+ 1G>A/ c.2846A>T compound heterozygous	10-25	Consider alternate therapy* (raltitexed or trifluridine/tipiracil). Centres with expertise and therapeutic drug monitoring may consider a starting dose of 10% of the target dose. If tolerant after the first cycle, titrate dose increases against toxicity over subsequent cycles to a maximum of 25% of the target dose.
c.1236G>A/HapB3/c.2846A>T compound heterozygous or c.2846A>T/c.2846A>T homozygous	10-50	Consider alternate therapy* (raltitexed or trifluridine/tipiracil). Centres with expertise and therapeutic drug monitoring may consider 10% of the target dose. If tolerant after the first cycle, titrate dose increases against toxicity over subsequent cycles to a maximum of 50% of the target dose.
c.1905+ 1G>A/c.1905+ 1G>A homozygous or c.1679T>G/ c.1679T>G homozygous or c.1905+ 1G>A/ c.1679T>G compound heterozygous	0	Complete DPD deficiency: do not use fluoropyrimidine therapy for any of these genotypes Recommend use of raltitrexed or trifluridine/tipiracil or alternate therapy*.
c.1679T>G/c.2846A>T compound heterozygous or c.1905+ 1G>A/HapB3DPYD compound heterozygous or c.1679T>G/HapB3DPYD compound heterozygous	10-25	Consider alternate therapy* (raltitexed or trifluridine/tipiracil). Centres with expertise and therapeutic drug monitoring may consider 10% of the target dose. If tolerant after the first cycle, titrate dose increases against toxicity over subsequent cycles to a maximum of 25% of the target dose.

Table 2. Recommended dose reduction for homozygous and compound heterozygous variant *DPYD* genotypes.continued

Homozygous and compound heterozygous genotypes	% DPD activity	Recommended dose adjustment
HapB3DPYD/HapB3DPYD homozygous or c.2846A>T/HapB3DPYD compound heterozygous	10-50	Consider alternate therapy* (raltitexed or trifluridine/tipiracil). Centres with expertise and therapeutic drug monitoring may consider 10% of the target dose. If tolerant after the first cycle, titrate dose increases against toxicity over subsequent cycles to a maximum of 50% of the target dose.

* The choice of dose reduced fluoropyrimdine or alternate therapy will be informed by the tumour type, clinical indication and predicted severity of enzyme deficiency based on DPYD genotype. When alternative therapy is recommended the suggested alternate therapy (raltitrexed or trifluridine/tipiracil) is appropriate where the treating oncologist considers the inclusion of an anti-metabolite the optimal therapeutic option. It is beyond the scope of this guideline to state the appropriate decision for each indication.

Further information:

Please contact Dr Paul Ross (Paul.Ross@gstt.nhs.uk) or Dr Tony Marinaki (Tony.Marinaki@viapath.co.uk) for questions or advice on this protocol.

Disclaimer:
The information contained in this guidance is a consensus of the development and consultation groups' views on current treatment. It should be used in conjunction with any local policies/procedures/guidelines and should be approved for use according to the trust clinical governance process. Care has been taken in the preparation of the information contained in the guidance. Nevertheless, any person seeking to consult the guidance, apply its recommendations or use its content is expected to use independent, personal medical and/or clinical judgement in the context of the individual clinical circumstances, or to seek out the supervision of a qualified clinician. The group makes no representation or guarantee of any kind whatsoever regarding the guidance content or its use or application and disclaim any responsibility for its use or application in any way.

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