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National Clinical Guidelines Addressing DPYD Screening and Genetic Counselling Prior to Fluoropyrimidines (FU)-Based Chemotherapy

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Abstract

Fluoropyrimidines (FU) (5-fluorouracil, capecitabine and the oral prodrug tegafur {not marketed in Saudi Arabia) are a commonly used chemotherapeutic agents to treat a wide variety of cancers. Fluoropyrimidines 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 well tolerated. However, severe adverse drug reactions have been recognised to occur in 5%-10% of the treated population. A considerable proportion of adverse drug reactions are likely to be the result of inter-individual genetic variation.

Keywords: Fluoropyrimidines • Oesophago-gastric • Pancreatic cancer • Population

Description

These drugs are primary detoxified by the hepatic enzyme Dihydropyrimidine Dehydrogenase (DPD) which is encoded by DPYD gene. The most well-known biochemical cause of intolerance to FU is a deficiency in DPD enzyme. Carriers of certain variants (polymorphism) in DPYD gene can result in reduced or even absent DPD enzyme activity, increasing the risk of severe, life threatening toxicity following treatment with standard doses. Four variants are currently considered clinically actionable: DPYD*2A, DPYD*13, c. 2846A>T and c.1236G>A. Symptoms of partial or complete deficiency include neutropenia, nausea, vomiting, diarrhea, stomatitis mucositis and hand foot syndrome. Toxicity is fatal in 1% of patients [1]. It is noteworthy to mention that these four variants forming the foundation of the current pharmacogenetic guidelines has been based on clinical studies conducted in populations of limited diversity, of European descent (Caucasians) [2]. Despite the finding that many patients have wild-type genotype for the classic four variants; the toxicity may still prevail in patients taking FU. Therefore, the search for additional DPYD variants associated with toxicity may improve the safety of treatment with FU specifically in Saudi population.

Novel variants in DPYD will continue to be identified with the introduction of Next-Generation Sequencing (NGS) techniques which systemic treatment with FU drugs. Patients with a known complete DP is used for routine clinical practice. In summary, Patients who will undergo FU-based chemotherapy might develop toxicity unless they are genetically screened for DPYD variants. Recent studies have shown that the cost of managing patients with severe toxicity and with DPYD positive test is higher than the cost of the prospective DPYD testing of each new patient commencing FU treatment. These results therefore showed that tests for the detection of DPYD variants is a cost-effective strategy. This document is meant to help in establishing a national clinical guideline addressing DPYD screening and genetic counselling prior to FU-based chemotherapy [3]. EMA recommended testing all patients for DPD deficiency prior to systemic treatment with FU drugs. Patients with a known complete DPD deficiency must not be given FU. As for patients with a partial DPD deficiency, a reduced starting dose should be considered. The EMA's recommendations have been adopted by the Federal Institute for Drugs and Medical Devices in Germany, and other scientific medical associations from Germany, Austria, and Switzerland have developed proposals for implementing EMA recommendation. Moreover, Dutch Pharmacogenetics Working Group (DPWG) published guideline concluded that DPYD genotyping is considered "essential" and has directed to do DPYD testing prior to initiating FU [4]. The recommendation stated that both pre-treatment testing for DPD genotyping (of the previously mentioned four variants), and phenotyping (by measurement of blood uracil levels) are acceptable.

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National clinical guidelines

Each organisation should ensure there is a clear Standard Operating Procedure (SOPs) for requesting a DPD screening test.

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. Any patient who has not had a DPD test should be referred to the consultant prior to going ahead with treatment. 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 (Table 1) [5].

Clinical staff	Responsibility
Head of nursing	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.
other Prescribers	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.

Table 1. Responsibilities of the different clinical staff.

Information for patients

Treatment with fluorouracil, capecitabine or tegafur:

- Before starting cancer treatment with fluorouracil given by injection or infusion (drip), capecitabine, your doctor should do a test to check whether you have a working DPD enzyme.
- If you have a known complete lack of DPD, you will not be given these treatments as they will increase the risk of severe and life-threatening side effects.
- If you have a partial DPD deficiency, your doctor may start treatment at low doses, which can be increased if there are no serious side effects.
- If you know that you have a partial DPD deficiency or if you have a family member who has partial or complete DPD deficiency, talk to your doctor or pharmacist before taking these medicines.
- If you have any questions about your treatment or about DPD testing, talk to your doctor or pharmacist.

Conclusion

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 should be considered. Dose levels can cautiously be increased subsequently as determined by toxicity levels. There are 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. Further test can be conducted to test the presence of rarer variants.

References

1. Hamzic, Seid, Aebi Stefan, Joerger Markus, and Montemurro Michael, et al. "Fluoropyrimidine Chemotherapy: Recommendations for DPYD Genotyping and Therapeutic Drug Monitoring of the Swiss Group of Pharmacogenomics and Personalised Therapy." *Swiss Med Weekly* 150 (2020).
2. Gross, Eva, Busse Birgit, Riemenschneider Matthias, and Neubauer Steffi, et al. "Strong Association of a Common Dihydropyrimidine Dehydrogenase Gene Polymorphism with Fluoropyrimidine-Related Toxicity in Cancer Patients." PloS One 3 (2008): e4003.
3. Murphy, Con, Byrne Stephen, Ahmed Gul, and Kenny Andrew, et al. "Cost Implications of Reactive Versus Prospective Testing for Dihydropyrimidine Dehydrogenase Deficiency in Patients with Colorectal Cancer: A Single-Institution Experience." Dose-Response 16 (2018): 1559325818803042.
4. Conti, Valeria, De Bellis Emanuela, Manzo Valentina, and Sabbatino Francesco, et al. "A Genotyping/Phenotyping Approach with Careful Clinical Monitoring to Manage the Fluoropyrimidines-Based Therapy: Clinical Cases and Systematic Review of the Literature." J Personal Med 10 (2020): 113.
5. Amstutz, Ursula, Froehlich Tanja K, and Largiadèr Carlo R. "Dihydropyrimidine Dehydrogenase Gene as a Major Predictor of Severe 5-Fluorouracil Toxicity." *Pharmacogenomics* 12 (2011): 1321-1336.

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