Template Monitoring for DPD deficiency in Capecitabine and 5-fluorouracil patients

Background

Dihydropyrimidine dehydrogenase (DPD) plays an important role in the metabolism of fluoropyrimidine drugs e.g. fluorouracil (5FU) and capecitabine. Patients with DPD deficiency may be predisposed to experience increased or severe toxicity when receiving 5-FU or capecitabine, and in some cases these events can be fatal.

It is estimated the incidence of DPD deficiency within the UK population can be up to 5%.(1). There is no routine NHS approved screening test for DPD deficiency, therefore any patients that experience severe or prolonged adverse events related to 5FU or capecitabine should be treated promptly with maximum supportive care.

Rationale

As there NHS funded no way to screen patients for DPD toxicity, clinical staff must be extra vigilant for signs of increased toxicity when starting a patient on a fluoropyrimidine. One strategy is to adopt additional monitoring for all patients who start on capecitabine or fluorouracil to ensure they are not experiencing undue levels of toxicity. In addition all patients starting on capecitabine patients could be reviewed during their 1st cycle to ensure they are not experiencing unusual toxicity so the drug can be stopped early in the cycle as appropriate.

Using this Template

This guidance was originally introduced in Northumbria Healthcare Trust and has been shared with members of Northern Cancer Alliance (NCA) Chemotherapy Group as part of learning from cases of DPD toxicity.

It is recommended that any organisation wishing to adopt an enhanced DPD toxicity monitoring process can review and adapts the guidance below and produce a local organisational guideline which must be reviewed and approved via local governance process of your organisation.

Organisations must note that following the process outlined below will not mitigate the risk of toxicity due to DPD deficiency and hence its suitability should be assessed in each organisation.

Acknowledgement

If the guidance of this document is adopted for local use, please include acknowledgement of source of document NCA Chemotherapy Group/ Northumbria Trust. March 2018. Link: https://www.northerncanceralliance.nhs.uk/advisory_group/chemotherapy-expert-advisory-group/

1 Monitoring for DPD Deficiency

1.1 Prescribers who consent patients for fluoropyrimidine drugs should ensure that these patients are specifically informed of the risk severe side effects, including death from these fluoropyrimidine drugs if patients have a deficiency of DPD. Other rare side effects may also be discussed.

1.2 The nursing staff must ensure that patients are given a printed copy of the DPD patient information leaflet from cancer research UK before commencing treatment. Leaflet is available at http://www.cancerresearchuk.org/about-cancer/cancer-in-general/treatment/chemotherapy/side-effects/dpd-deficiency-and-fluorouracil

1.3 All patients fluoropyrimidine must be given a phone call 48 to 72 hours after starting treatment to check they are not experiencing undue toxicity. If during the phone call there is any concern about patient advise them to report Oncology day unit as soon as possible that day for face to face review and toxicity assessment.

1.4 Ensure patient is informed of action to take if signs of toxicity (e.g. severe mucositis, diarrhoea) develop within the first few days of treatment, as this is often an early indication of DPD deficiency.

1.5 All new capecitabine patients should be asked to attend ward for day 8 review on the first cycle (both combination and single agent regiments) unless they have previously had a fluoropyrimidine without undue toxicity (see 1.8).

1.6 Depending on the regimen and outcome of telephone call 48 to 72 hours after starting fluorouracil patients may be asked to return for a day 8 toxicity assessment.

1.7 The day 8 review must include toxicity assessment and check of FBC. Ask patients to bring their capecitabine with them and assess if safe to continue treatment.

1.8 If patient has previously has a course of capecitabine or 5-fluorouracil (in the last 12 months) without undue toxicities then they are unlikely to be DPD deficiency so a telephone phone consultation call can be arranged for day 8 instead of ward attendance.

1.9 If patient is experience side effects and blood counts are abnormal (e.g. PLT <50 and ANC <1.0) stop treatment and refer back to consultant

1.10 If patient is experience side effects but blood counts are normal, then a clinical judgment must be made to

- ***either*** stop treatment and refer back to consultant
- ***or*** allow patient to continue with treatment but under closer supervision, i.e. instructed to stop if side effects worsen and a day 15 phone call is arranged.

1.11 From cycle two onwards if not problems then revert to standard assessment schedule as per regimen.

2 Testing for DPD deficiency in capecitabine or fluorouracil patients.

2.1 There is currently no test for DPD toxicity that is approved and funded by the NHS. There are commercial tests available from private laboratories that look for changes in the DYPD gene. However because of the range of Pharmacogenetic variation on the DYPD gene, tests may not identify all people who have DPD toxicity and hence have not been adopted as standard NHS practice.

2.2 Viapath are a commercial provider of tests that will undertake DPD testing for five polymorphic variants in the DPYD gene as a diagnostic test to predict fluoropyrimidine toxicity, the test has been reported as been adopted for selected patients at least one UK centre.2

2.3 Testing is not routinely offered in the Trust, however patients are made aware that testing is possible as part of the provision of patient information, see 2.x,

3 Management of Toxicity due to DPD deficiency

3.1 If a patient experiences toxicity and is suspected of DPD deficiency then treatment is based on firstly ensuring that they have stopped the capecitabine or 5-fluorouracil.

3.2 As there is no specific treatment for DPD induced toxicity, treatment consists of Then it consists managing each specific symptom and providing general medical support, monitoring for signs of toxicity

3.2 There is a drug in development (at time of writing) that in future may be available as treatment for DPD toxicity (Vistogard ® Uridine Triacetate), whilst this is available in the USA this is not available in Europe and the UK at this time, it is expected to be licensed in UK in 2019. The drug is an oral prodrug of uridine which reduces incorporation of fluorouracil metabolites into genetic material on non-cancerous cells. (source www.sps.nhs.uk)

References

1. Deenen MJ, et al. Upfront Genotyping of DPYD*2A to Individualize Fluoropyrimidine Therapy: A Safety and Cost Analysis. Journal of Clinical Oncology 34, no. 3 (January 2016) 227-234

2. Davies L, Morris E, Bayliss K BOPA 2017 Abstract 37: DPD deficiency testing – An overview of current variations in practice. Journal of Oncology Pharmacy Practice 23 8 Supplement P34

3. DPD deficiency in patients treated with fluorouracil Ciccolini, Joseph. The Lancet Oncology , Volume 16 , Issue 16 , 1574 - 1576