**Systemic Anti Cancer Treatment Protocol**

# Temozolomide & Capecitabine

**PROTOCOL REF: MPHATECAGA**
**(Version No: 1.1)**

## Approved for use as an interim measure during COVID-19 pandemic

## Approved for use in:

Second-line treatment of high grade neuroendocrine cancer

### Cautions / Contra-indications

Capecitabine: Caution in patients with pre-existing heart disease, angina pectoris, arrhythmias or taking high dose aspirin or coumarin anticoagulants

Capecitabine: DPD deficiency – leads to severe early fluorouracil toxicity, affects approximately 3% of population, may be life threatening

## Dosage:

| Drug | Dosage | Route | Frequency |
|---|---|---|---|
| Capecitabine | 750mg/m$^2$ BD | PO | Day 1 to14 of 4 week cycle |
| Temozolomide | 200mg/m$^2$ ON | PO | Day 10 to14 inclusive of 4 week cycle |

**Repeated every 4 weeks until disease progression or intolerance**

### Supportive treatments:

Ondansetron 8mg daily on Day 10 to 14 inclusive taken 1 hour prior to Temozolomide

Domperidone 10mg three times daily when required

**OR**

Cyclizine 50mg three times daily when required

Loperamide 2mg prn after each loose stool

## Administration:

**Counselling points:**

| **Capecitabine** |
|---|
| Available as 150mg and 500mg tablets.<br>Tablets should be taken 12 hours apart.<br>Swallow whole with water within 30 minutes after a meal.<br>Only take missed doses if remembered within 2 hours of the normal scheduled time.<br>In case of swallowing difficulties the tablets may be dissolved in 200mL warm water (boiled and cooled). Once dissolved stir the contents with a spoon and drink immediately. Wash well and reserve the glass and spoon for chemotherapy administration only. |
| **Temozolomide** |
| Available as 5mg, 20mg, 100mg, 140mg, 180mg and 250mg capsules.<br>Ondansetron should be taken 1 hour before Temozolomide.<br>Temozolomide should be taken on an empty stomach either 2 hours before food or 1 hour after.<br>Swallow whole with water.<br>Only take missed doses if remembered within 12 hours of the normal scheduled time.<br>In case of swallowing difficulties instructions on how to produce a mixture is available at https://www.gosh.nhs.uk/medical-information-0/medicines-information/temozolomide |
| **General Points** |
| Do not double up missed doses.<br>Do not add doses missed onto the end of the cycle. Continue according to the treatment plan and stop taking on the originally scheduled day. |

## Drug Interactions

| Capecitabine |
| --- |
| Allopurinol – reduced efficacy of capecitabine – avoid.<br>Clozapine – additive risk of agranulocytotis.<br>Folic acid – increased risk of side effects of capecitabine, avoid if possible – discuss with pharmacy.<br>Phenytoin – potentially toxic levels of phenytoin have been reported- monitor carefully<br>Warfarin and other coumarin anticoagulants – increased bleeding risk, monitor INR carefully, consider switch to LMWH. |
| **Temozolomide** |
| None reported. |

## Main Toxicities:

| Capecitabine |
| --- |
| Myelosuppression, diarrhoea, Palmar Plantar Erythema (PPE or hand- foot syndrome), stomatitis, fatigue, asthenia, anorexia, cardiotoxicity (uncommon), ovarian failure/infertility, increased renal dysfunction on those with preexisting compromised renal function, and thrombosis/embolism. |
| **Temozolomide** |
| Myelosuppresion (thrombocytopenia and neutropenia), fatigue, alopecia, nausea and vomiting, anorexia, rash (if severe allergic can require discontinuation), headaches, constipation, Hepatotoxicity (rare fatal cases have been reported), amenorrhoea, loss of fertility, pneumocystis carinii pneumonia. |

## Investigations and treatment plan

| | Pre | Cycle 1 Day 1 | Cycle 1 Day 15 | Cycle 2 | Cycle 3 | Ongoing |
|---|---|---|---|---|---|---|
| Medical Assessment | X | | X | X | X | At end of treatment |
| Nursing Assessment | X | X | X | X | X | Every cycle |
| FBC | X | X | X | X | X | Every cycle |
| U&E, LFT, Mg2+ | X | X | X | X | X | Every cycle |
| CrCl (Cockroft and Gault) | X | X | X | X | X | Every cycle |
| Dihydropyrimidine dehydrogenase (DPD) deficiency test | X | | | | | This test is normally only required if a patient has not had capecitabine, or fluorouracil in the past. However a consultant may still request this test if capecitabine or fluorouracil was not tolerated previously. The result must be available before administration of chemotherapy unless clear documentation from the consultant is available to the contrary. Treatment with capecitabine and fluorouracil is contraindicated in patients with known complete DPD deficiency. |
| CT scan | X | | | | X | As clinically indicated |
| Informed Consent | X | | | | | |
| ECG | X | | | | | If clinically indicated |
| Blood pressure measurement | X | | | | | Repeat if clinically indicated |
| PS recorded | X | X | X | X | X | Every cycle |
| Toxicities documented | X | X | X | X | X | Every cycle |
| Weight recorded | X | X | X | X | X | Every cycle |

## Dose Modifications and Toxicity Management:

### Haematological toxicity

Proceed on day 1 if:-

| | |
|---|---|
| ANC ≥ 1.0 x $10^9$/L | Platelets ≥ 100 x $10^9$/L |

### Capecitabine dose adjustment guidelines

| Common Toxicity Criteria / Haematological Parameter | Dose changes within a treatment cycle | Dose adjustment for next cycle/dose(% of starting dose) |
|---|---|---|
| Grade 1 | Maintain dose level | Maintain dose level |
| Grade 2 | | |
| -1st appearance | Interrupt until resolved to grade 0-1 | 100% (for PPE give 85% dose)* |
| -2nd appearance | | 75% |
| -3rd appearance | | 50% |
| -4th appearance | Discontinue treatment permanently | Not applicable |
| Grade 3 | | |
| -1st appearance | Interrupt until resolved to grade 0-1 | 75% (for PPE give 70% dose)* |
| -2nd appearance | | 50% |
| -3rd appearance | Discontinue treatment permanently | Not applicable |
| Grade 4 | | |
| -1st appearance | Discontinue permanently Or If physician deems it to be in the patient's best interest to continue, interrupt until resolved to grade 0-1 | 50% (consultant approval only) |
| -2nd appearance | Discontinue permanently | Not applicable |

### Non-haematological toxicity

**Renal**

Capecitabine

Calculate CrCl using Cockroft and Gault formula at baseline and before each cycle and adjust dose according to table.

| Creatinine Clearance (mL/min) | Capecitabine Dose | Oxaliplatin Dose |
|---|---|---|
| Above 50 | Give 100% | Give 100% |
| 30 to 50 | Give 75% | Give 100% |

| | | | | |
|---|---|---|---|---|
| | Below 30 | Omit | Omit | |
| Temozolomide | No dose adjustment required | | | |

| **Hepatic** | |
|---|---|
| Capecitabine | <table><tr><th>**Bilirubin (mmol/L)**</th><th>**Epirubicin dose**</th></tr><tr><td>24 to 51</td><td>50%</td></tr><tr><td>52 to 85</td><td>25%</td></tr><tr><td>Above 85</td><td>Omit</td></tr></table> Capecitabine – If ALT/AST > 2 x ULN or Bilirubin > 3 x ULN – omit until recovery |
| Temozolomide | No dose adjustments necessary for mild to moderate hepatic impairment. Consider effects of concurrent medication on hepatic function.<br>Stop temozolomide if there is a progressive rise in transaminases or rise in bilirubin |

**Other Capecitabine Toxicity**

| | |
|---|---|
| **Diarrhoea** | Treat symptomatically with Loperamide at standard doses, codeine may be added. If persistent or grade 3 or 4 stop capecitabine until resolved to grade 0 or 1. Restart as per CTC table above for dose reductions |
| **Stomatitis** | Regular mouthwashes (water, saline or non alcoholic proprietary brand), brush gently with a soft brush, adequate pain relief, nutritional support in severe cases – see above for dose reductions. |
| **PPE** | Manage as per trust policy, withhold treatment until resolved to grade 1, dose reductions as per CTC table above. |
| **Conjunctivitis** | Eye drops for symptomatic treatment |
| **Chest Pain / coronary artery spasm** | Stop capecitabine, standard angina investigations, refer to consultant, if symptoms persist stop capecitabine permanently |

## References:

Olsen IH, Sorenson JB, Federspiel B et al. Temozolomide as Second or Third Line Treatment of Patients with Neuroendocrine Carcinomas. *The Scientific World Journal* Vol2012 Art ID 170496. 2012

Welin S, Halfdan, Sebjornsen S et al. Clinical Effect of Temozolomide-Based Chemotherapy in Poorly Differentiated Endocrine Carcinoma after Progression on First-Line Chemotherapy

Strosbery JR, Fine RL, Choi J et al. First-Line Chemotherapy with Capecitabine and Temozolomide in Patients with Metastatic Pancreatic Endocrine Carcinomas. *Cancer*. 2011

Electronic Medicines Compendium, Xeloda 150mg and 500mg film-coated tablets, https://www.medicines.org.uk/emc/medicine/4619

Electronic Medicines Compendium, Temozolomide 100mg hard capsules, https://www.medicines.org.uk/emc/product/5318