# Gemcitabine (1000mg/m$^2$) and Capecitabine (650mg/m$^2$) Therapy- 21 day[i]

## INDICATIONS FOR USE:

| INDICATION | ICD10 | Regimen Code | Reimbursement status |
|---|---|---|---|
| Locally advanced or metastatic pancreatic carcinoma | C25 | 00384a | Gemcitabine – Hospital<br>Capecitabine - CDS |
| Locally advanced biliary tree carcinoma | C23 | 00384b | |

## TREATMENT:

*The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.*

Gemcitabine is administered on day 1 and day 8 and capecitabine is taken on day 1-14 of a 21 day cycle until disease progression or unacceptable toxicity develops

Facilities to treat anaphylaxis MUST be present when the chemotherapy is administered.

| Day | Drug | Dose | Route | Diluent & Rate |
|---|---|---|---|---|
| 1 and 8 | Gemcitabine | 1000mg/m$^2$ | IV infusion | 250ml NaCl 0.9% over 30mins |
| 1 -14 | Capecitabine[a,b] | 650mg/m$^2$ Twice Daily[c] | PO with food | N/A |
| [a]The dose to be administered should consider the available tablet strengths.<br>Reference the NCCP DOSE BANDING TABLES here for guidance on dosing of capecitabine<br>Tablets should be swallowed whole with plenty of water within 30 minutes of eating. Tablets should not be crushed or cut. | | | | |
| [b] See dose modifications section for patients with identified partial DPD deficiency | | | | |
| [c](Total daily dose = 1300mg/m$^2$) | | | | |

## ELIGIBILITY:

- Indications as above
- ECOG 0-2

## EXCLUSIONS:

- Hypersensitivity to gemcitabine, capecitabine or any of the excipients
- Known complete DPD deficiency
- History of severe and unexpected reactions to fluoropyrimidine therapy
- Pregnancy and lactation
- Severe hepatic or renal impairment

## PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist

## TESTS:

**Baseline tests**:

- FBC, renal and liver profile
- DPD testing prior to first treatment with capecitabine using phenotype and/or genotype testing unless patient has been previously tested

**Regular tests**:

- Day 1: FBC, renal and liver profile
- Day 8: FBC

**Disease monitoring:**
Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

## DOSE MODIFICATIONS:

- Consider a reduced starting dose in patients with identified partial DPD deficiency.
  - Initial dose reduction may impact the efficacy of treatment. In the absence of serious toxicity, subsequent doses may be increased with careful monitoring.
- Any dose modification should be discussed with a Consultant.

### Haematological:

Prior to commencing a new treatment cycle (i.e. day 1), ANC must be ≥1 x $10^9$/L and platelets ≥ 100 x$10^9$/L.

**Table 1: Dose modifications for gemcitabine and capecitabine within a cycle**

| ANC (x $10^9$ /L) | | Platelet count (x $10^9$ /L) | | Other toxicity | Recommended dose of Gemcitabine | Recommended dose of Capecitabine |
|---|---|---|---|---|---|---|
| ≥1 | and | ≥100 | | | 100 % | 100% |
| 0.5- 1 | or | 50-100 | | | 75% | 100% |
| < 0.5 | or | <50 | | | Omit. Do not restart treatment until ANC ≥ 0.5 and platelets ≥ 50 | Interrupt treatment until recovery of toxicity to ≤ Grade 1 |
| ANC < 0.5 for ≥ 5 days **or** ANC < 0.1 for ≥ 3 days **or** Any incidence of febrile neutropenia | **or** | < 25 | **or** | cycle delay of >1 week due to any toxicity | Reduce dose to 75% of the original cycle initiation dose for all subsequent cycles. | Interrupt treatment until recovery of toxicity to ≤ Grade 1 |

## Renal and hepatic impairment:

**Table 2: Dose modifications for capecitabine and gemcitabine in renal and hepatic impairment**

| Drug | Renal Impairment | | Hepatic Impairment |
|---|---|---|---|
| Capecitabine* | **Creatinine Clearance (CrCl ml/min)** | **Dose** | In the absence of safety and efficacy data in patients with hepatic impairment, capecitabine use should be carefully monitored in patients with mild to moderate liver dysfunction, regardless of the presence or absence of liver metastasis. |
| | ≥30 | 100% | |
| | <30 | Omit | |
| Gemcitabine | ≥ 30 | 100% | AST levels do not seem to cause dose limiting toxicities.<br>If bilirubin > 27micromol/L, initiate treatment with dose of 800mg/m$^2$ |
| | <30 | Consider dose reduction – clinical decision. | |
| *Reference Table 7 for dose modification of capecitabine in treatment related hepatotoxicity | | | |

## Management of adverse events:

**Table 3: Dose Modification of gemcitabine for Adverse Events**

| Adverse reactions | Recommended dose modification of gemcitabine |
|---|---|
| Grade ≥ 2 Pneumonitis | **Discontinue gemcitabine** |
| Grade > 3 Non-haematological toxicity (except nausea/vomiting) | Therapy with gemcitabine should be withheld (until toxicity has resolved to grade ≤ 1) and may be resumed with 50% dose reduction or treatment discontinued at discretion of prescribing consultant. |
| Grade > 4 Non-haematological toxicity | Discontinue treatment |

**Table 4: Dose Modification of Capecitabine for Adverse Events**

| Toxicity grades* | 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% |
| • 2nd appearance | | 75% |
| • 3rd appearance | | 50% |
| • 4th appearance | Discontinue permanently | |
| **Grade 3** | | |
| • 1st appearance | Interrupt until resolved to grade 0-1 | 75% |
| • 2nd appearance | | 50% |
| • 3rd appearance | Discontinue permanently | |
| **Grade 4** | | |
| • 1st appearance | Discontinue permanently<br>or<br>If consultant deems it to be in patient's best interest to continue, interrupt until resolved to grade 0-1 | 50% |
| • 2nd appearance | Discontinue permanently | |
| Medication may be required for management of diarrhoea, e.g. loperamide (4mg at first onset followed by 2mg after each loose stool (max 16 mg /day) or see local policy | | |

*Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

**Table 5: Dose Modification of capecitabine for diarrhoea**

| Grade | Diarrhoea | Dose changes within a treatment cycle | Dose adjustment for next cycle/dose (% of starting dose) |
|---|---|---|---|
| 0-1 | Increase of 2 to 3 stools/day or nocturnal stools | Maintain dose level | Maintain dose level |
| 2 | Increase of 4 to 6 stools/day or nocturnal stools | | |
| | • 1st appearance | Interrupt until resolved to grade 0-1 | 100% |
| | • 2nd appearance | | 75% |
| | • 3rd appearance | | 50% |
| | • 4th appearance | Discontinue permanently | |
| 3 | Increase of 7 to 9 stools/day or incontinence | | |
| | • 1st appearance | Interrupt until resolved to grade 0-1 | 75% |
| | • 2nd appearance | | 50% |
| | • 3rd appearance | Discontinue permanently | |
| 4 | Increase of 10 or more stools/day or grossly bloody diarrhoea; may require parenteral support | | |
| | • 1st appearance | Discontinue permanently<br>or<br>If consultant deems it to be in patient's best interest to continue, interrupt until resolved to grade 0-1 | 50% |
| | • 2nd appearance | Discontinue permanently | |
| Medication may be required for management of diarrhoea, e.g. loperamide (4mg at first onset followed by 2mg after each loose stool (max 16 mg /day) or see local policy | | | |

## Hand foot syndrome:

**Table 6: Dose modification of capecitabine in hand foot syndrome**

| Toxicity Grade | | Dose Modification |
|---|---|---|
| Grade 1 | Skin changes (e.g., numbness, dysesthesia, paraesthesia, tingling, erythema) with discomfort not disrupting normal activities | 100% Dose |
| Grade 2 | Skin changes (e.g., erythema, swelling) with pain affecting activities of daily living | Withhold treatment until event resolves or decreases in intensity to grade 1. |
| Grade 3 | Severe skin changes (e.g., moist desquamation, ulceration, blistering) with pain, causing severe discomfort and inability to work or perform activities of daily living | Withhold treatment until event resolves or decreases in intensity to grade 1. Subsequent doses of capecitabine should be decreased |

**Treatment related hepatotoxicity**

**Table 7: Dose modification of capecitabine in treatment related hepatotoxicity**

| Bilirubin | | ALT, AST | Dose Modification |
|---|---|---|---|
| > 3.0 x ULN | **or** | > 2.5 x ULN | Withhold treatment until bilirubin decreases to ≤ 3.0 x ULN or ALT, AST decrease to ≤ 2.5 x ULN |

## SUPPORTIVE CARE:

**EMETOGENIC POTENTIAL:** Low (**Refer to local policy).**

**PREMEDICATIONS:** Not usually required

**OTHER SUPPORTIVE CARE**:

Medication may be required for management of diarrhoea, e.g. loperamide (4mg at first onset followed by 2mg after each loose stool (max 16 mg /day) **(refer to local policy)**

## ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

*The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details*.

- **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated appropriately.

**Gemcitabine:**

- **Pulmonary Toxicity**: Acute shortness of breath may occur. Discontinue treatment with gemcitabine if drug-induced pneumonitis is suspected.
- **Cardiovascular:** Due to the risk of cardiac and/or vascular disorders with gemcitabine, particular caution must be exercised with patients presenting a history of cardiovascular events.
- **Haemolytic Uremic syndrome:** Irreversible renal failure associated with hemolytic uremic syndrome may occur (rare) with Gemcitabine. Use caution with pre-existing renal dysfunction.

**Capecitabine:**

- **Diarrhoea and dehydration:** This may be dose limiting with capecitabine therapy**.** Patients with severe diarrhoea should be carefully monitored and given fluid and electrolyte replacement if they become dehydrated.
- **Cardiotoxicity:** Angina-like chest pain, tachycardia, arrhythmias, heart failure, myocardial infarction and cardiac arrest may occur with capecitabine especially in patients with a prior history of coronary artery disease.
- **Dihydropyrimidine dehydrogenase (DPD) deficiency:** DPD is an enzyme encoded by the DPYD gene which is responsible for the breakdown of fluoropyrimidines. Patients with DPD deficiency are therefore at increased risk of fluoropyrimidine-related toxicity, including for example stomatitis, diarrhoea, mucosal inflammation, neutropenia and neurotoxicity. Treatment with 5-Fluorouracil, capecitabine or tegafur-containing medicinal products is contraindicated in patients with known complete DPD deficiency. Consider a reduced starting dose in patients with identified partial DPD deficiency. Initial dose reduction may impact the efficacy of treatment. In the absence of serious toxicity, subsequent doses may be increased with careful monitoring. Therapeutic drug monitoring (TDM) of fluorouracil may improve clinical outcomes in patients receiving continuous 5-fluorouracil infusions.

- **Hand-foot syndrome (HFS)**, also known as palmar-plantar erythrodysaesthesia (PPE), is a common side effect associated with capecitabine (see Table 6 for dose modification of capecitabine for HFS).

## DRUG INTERACTIONS:

- Capecitabine enhances the anticoagulant effect of warfarin. Patients taking coumarin derivative anticoagulants should be monitored regularly for alterations in their coagulation parameters and the anti-coagulant dose adjusted accordingly.
- Sorivudine inhibits dihydropyrimidine dehydrogenase thus increasing its toxicity. Therefore capecitabine must not be administered concomitantly with sorivudine or its chemically related analogues.
- Patients taking phenytoin or fosphenytoin concomitantly with capecitabine should be regularly monitored for increased phenytoin plasma concentrations.
- Current drug interaction databases should be consulted for more information.

## ATC CODE:

| | |
|---|---|
| Gemcitabine | L01BC05 |
| Capecitabine | L01BC06 |

## REFERENCES:


1. Knox J, Hedley D, Oza A. et al. Combining Gemcitabine and Capecitabine in Patients with Advanced Biliary Cancer: A phase 11 Trial. Journal of Clinical Oncology 2005;23(10), 2332-2338
2. HPRA Direct Healthcare Professional Communication. 5-Fluorouracil (i.v.), capecitabine and tegafur containing products: Pre-treatment testing to identify DPD-deficient patients at increased risk of severe toxicity. Accessed Aug 2020 Available at: https://www.hpra.ie/docs/default-source/default-document-library/important-safety-information-from-marketing-authorisation-holders-of-products-containing-5-fluorouracil-(i-v-)-capecitabine-and-tegafur-as-approved-by-the-hpra.pdf?sfvrsn=0
3. Gemcitabine 40 mg/ml Concentrate for Solution for Infusion Summary of Product Characteristics Accessed Sept 2020. Available at http://www.hpra.ie/img/uploaded/swedocuments/LicenseSPC_PA0405-080-001_08092015123059.pdf
4. Xeloda®Summary of Product Characteristics Accessed Sept 2020. Available at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000316/WC500058151.pdf

| Version | Date | Amendment | Approved By |
|---|---|---|---|
| 1 | 20/12/2016 | | Prof Maccon Keane |
| 2 | 10/09/2018 | Applied new NCCP regimen template. Updated title and exclusions with respect to DPD deficiency | Prof Maccon Keane |
| 3 | 17/10/2018 | Standardisation of dose modification tables ( hematological , renal and hepatic modifications and adverse events). Inclusion of dose modification tables for capecitabine | Prof Maccon Keane |
| 4 | 11/03/2020 | Updated capecitabine dosing in renal impairment | Prof Maccon Keane |
| 5 | 26/8/2020 | Reviewed.<br>Updated exclusion criteria, baseline testing, dose modifications and adverse events with respect to DPD deficiency as per DHPC from HPRA June 2020<br>Updated Adverse events regarding palmar-plantar erythrodysaesthesia | Prof Maccon Keane |

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] This regimen is outside its licensed indication in Ireland. Patients should be informed of the unlicensed nature of this indication and consented to treatment in line with the hospital's policy on the use of unlicensed medication and unlicensed or "off label" indications. Prescribers should be aware of their responsibility in communicating any relevant information to the patient and also in ensuring that the unlicensed or "off label" indication has been acknowledged by the hospital's Drugs and Therapeutics Committee, or equivalent, in line with hospital policy.
Further details on the Cancer Drug Management Programme is available at;
http://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/cdmp/