**Systemic Anti Cancer Treatment Protocol**

# Irinotecan & Capecitabine (14 day regimen) (I-Cap)

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

## Approved for use in:

Advanced colorectal cancer first line

Advanced colorectal cancer second line after oxaliplatin

Performance status 0-1

## Dosage:

| Drug | Dosage | Route | Frequency |
|---|---|---|---|
| Irinotecan | 180mg/m$^2$ | IV | Every 14 days |
| Capecitabine | 900mg/m$^2$ BD for 9 days | PO | Every 14 days |

Round doses to nearest whole dose using 150mg and 500mg tablets

**Supportive treatments:**

Emetic Risk – Moderate – follow antiemetic policy

Loperamide 4mg immediately after first liquid stool followed by 2mg every 2 hours for at least 12 hours

Domperidone 10mg oral tablets, up to 3 times a day or as required

Caution in patients with pre-existing coronary heart disease, angina pectoris, arrhythmias or those on high dose aspirin or coumarin anticoagulants

## Extravasation risk:

Irritant – Follow trust/network extravasation policy. No specific antidote needed but use cold compression +/- 1% hydrocortisone cream if symptoms warrant

## Administration:

| Day | Drug | Dosage | Route | Diluent and Rate |
|---|---|---|---|---|
| 1 | **Dexamethasone**<br>30 mins prior to chemotherapy | 8mg | PO | |
| 1 | **Ondansetron**<br>30 mins prior to chemotherapy | 16mg | PO | |
| 1 | **Atropine** | 600 micrograms | SC | Always prior to irinotecan |
| 1 | **Irinotecan** | 180 mg/m$^2$ | IV | 250mL glucose 5% over 30 to 90 minutes |
| Days 1 to 9 | **Capecitabine** | 900mg/m$^2$ BD | PO | Twice daily morning and evening |

Reassess after 6 cycles (12 weeks), then continue subject to patient choice, tolerability and response

**Notes:**

**Capecitabine**

Tablets are available in 500mg and 150mg strengths.

Counselling points:

Tablets should be taken 12 hours apart, morning and evening.

Swallow whole with water within 30 minutes of a meal

Do not add doses missed due to toxicity onto the end of the cycle. Continue according to the treatment plan and stop taking on the originally scheduled day.

Take missed doses if remembered within 2 hours of the normal scheduled time. Otherwise continue with the next scheduled dose. Do not double up missed doses

In case of swallowing difficulties the tablets may be dissolved in 200ml warm water. Once dissolved stir the contents with a spoon and drink immediately. Wash well and reserve the glass and spoon for chemotherapy administration only

**Drug Interactions**

**Capecitabine**

Allopurinol – reduced efficacy of capecitabine – avoid

Clozapine – additive risk of agranulocytotis

Folic acid – increased risk of side effects of capecitabine, avoid if possible – discuss with pharmacy

Phenytoin – potentially toxic levels of phenytoin have been reported- monitor carefully

Warfarin and other coumarin anticoagulants – increased bleeding risk, monitor INR carefully, consider switch to LMWH

## Main Toxicities:

**Irinotecan**

Myelosuppression, diarrhoea, alopecia, cholinergic syndrome during administration, ovarian failure/infertility

**Cholinergic syndrome**: Diarrhoea, sweating, blurred vision, dizziness within first 24 hours after irinotecan.

**Diarrhoea**: This may occur within 30-90 minutes of the infusion or may be delayed. Ensure patients are dispensed loperamide and that they know how and when to take them

Neutropenia with diarrhoea is a life threatening complication and requires immediate admission and management.

**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

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

## Investigations and treatment plan:

| | Pre | Cycle 1 | Cycle 2 | Cycle 3 | Cycle 4 | Ongoing |
|---|---|---|---|---|---|---|
| Medical Assessment | X | | X | | X | Alternate cycles |
| Nursing Assessment | X | X | X | X | X | Every cycle |
| FBC | X | X | X | X | X | Every cycle |
| U&E & LFT | X | X | X | X | X | Every cycle |
| CrCl | 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 | | | | | |
| Informed Consent | X | | | | | |
| 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 all apply:-

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

Delay 1 week on day 1 if any apply:-

| | |
|---|---|
| ANC ≤ 0.9 x $10^9$/L | Platelets ≤ 99 x $10^9$/L |

Note that in general the dose of the offending agent should be modified, however, if treatment is to be deferred for haematological toxicity then the whole regimen should be deferred to the following week.

If longer than 1 week delay or more than one consecutive cycle delay, upon recovery, reduce irinotecan and capecitabine doses by 20%. Continue on this dose unless further toxicity occurs. Further reductions should be discussed with the Consultant

### Non-haematological toxicity

**Renal**

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

| **Creatinine Clearance (mL/min)** | **Irinotecan Dose** | **Capecitabine Dose** |
|---|---|---|
| >50 | Give 100% | Give 100% |
| 30 to 50 | Give 100% | Give 75% |
| <30 | Use with caution | Omit |

No information on using irinotecan in severe renal impairment – discuss with consultant

**Hepatic**

| **Liver function** | **Irinotecan dose** | **Capecitabine dose** |
|---|---|---|
| Bilirubin 1.5 – 3 x ULN or ALP > 5 x ULN | 50% | – |
| Bilirubin > 3 x ULN | 50% | – |

| | | | |
|---|---|---|---|
| | Bilirubin > 3 x ULN or ALT/AST > 2.5 x xULN | _ | Omit capecitabine |
| | Note that significantly impaired hepatic function might be a sign of disease progression and require cessation or change of treatment.<br>**Always discuss deteriorating organ function with consultant** | | |

**Irinotecan**

| | |
|---|---|
| Diarrhoea | This may be due to irinotecan and / or Capecitabine. Always treat as irinotecan induced |
| Diarrhoea within first 24 hours | This is likely to be caused by an acute cholinergic syndrome, do not take loperamide within the first 24 hours. Advise patient to contact chemotherapy team and consider repeat dose of atropine |
| Delayed diarrhoea (after 24 hours post irinotecan) | Once a liquid stool occurs loperamide 4mg should be taken immediately, followed by 2mg every 2 hours for at least 12 hours, and for 12 hours following the last liquid stool.<br>Patients should be instructed to drink large volumes of water or electrolytes.<br>Do not continue high dose loperamide for longer than 48 hours<br>Any concomitant fever or vomiting will require hospitalisaton for rehydration<br>If diarrhea persists for 24 hours despite loperamide, start ciprofloxacin 250mg po bd for 7 days.<br>If diarrhoea persists after 48 hours then patients should be hospitalised for further management and treatment review.<br>Do **not** use loperamide prophylactically even if delayed diarrhoea occurred in previous cycles.<br>For first episode of diarrhoea grade 2 or higher, delay treatment for 1 to 2 weeks until completely resolved* and **reduce dose of irinotecan by 20% in subsequent cycles**.<br>(see table below for capecitabine adjustment) |

**Capecitabine**

| | |
|---|---|
| Diarrhoea | Loperamide at standard doses – ensure maximum dose reached, codeine may be added – see table below 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 below for dose reductions. |
| Palmar plantar erythema (PPE) or hand foot syndrome | Manage as per trust policy, withhold treatment until resolved to grade 1, dose reductions as per table below. |
| Sore eyes / Conjunctivitis | Eye drops for symptomatic treatment such as hypromellose 0.3% – avoid antimicrobial eyedrops unless indicated for infective conjunctivitis |
| Chest Pain / coronary artery spasm | Stop capecitabine, standard angina investigations, refer to consultant, if symptoms persist stop capecitabine permanently |

## Capecitabine Dose adjustment guidelines according to CTC

Including diarrhoea, vomiting, stomatitis, and PPE

| Common Toxicity Criteria | 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 treatment permanently | Not applicable |
| Grade 3 | | |
| -1st appearance | Interrupt until resolved to grade 0-1* | 75% |
| -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 |

## References:

Reinacher-Schick et al; JCO 2008;26 (15S): 4030

Summary of Product Characteristics, Electronic Medicines Compendium, Xeloda, https://www.medicines.org.uk/emc/medicine/4619 and irinotecan https://www.medicines.org.uk/emc/medicine/27592