CAPECITABINE RADIATION PROTOCOL
Cumbria, Northumberland, Tyne & Wear Area Team

DRUG ADMINISTRATION SCHEDULE

<table>
<thead>
<tr>
<th>Day</th>
<th>Drug</th>
<th>Daily Dose</th>
<th>Route</th>
<th>Diluent</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Up to 35 days continuously</td>
<td>Capecitabine</td>
<td>825mg/m² Twicely Daily *</td>
<td>Oral</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>whilst on radiotherapy</td>
<td></td>
<td></td>
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<td></td>
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</tbody>
</table>

COMMENTS ON SCHEDULE:
Various schedules for capecitabine chemoradiation exist; the above schedule has the largest evidence base. It is also possible to give capecitabine five days per week Monday to Friday whilst on radiotherapy at a dose of either 825mg/m² or 1000mg/m².

DOSE FORM
Capecitabine is supplied as 150mg and 500mg tablets, therefore calculated doses must be rounded to the nearest 150mg.

CYCLE LENGTH AND NUMBER OF DAYS
Radiotherapy: doses ranging from 45 Gy to 60 Gy given in 25 to 30 daily fractions Capecitabine 825 mg/m² twice daily from the first to the last day of radiotherapy (including weekends).

APPROVED INDICATIONS
Rectal cancer for patients whose disease needs down staging prior to surgery

ELIGIBILITY CRITERIA
Colorectal patients with adequate renal function (CrCl >30ml/min)

EXCLUSION CRITERIA
Patients incapable of managing oral chemotherapy themselves or with the assistance of a carer
- Patients with swallowing difficulties
- Patients with impaired renal function (CrCl <30ml/min)

PREMEDICATION
None

RECOMMENDED TAKE HOME MEDICATION
Metoclopramide 10mg three times daily as required

INVESTIGATIONS / MONITORING REQUIRED
Pre treatment: Assessment of renal function, FBC, Cardiac history, FBC, U&E’s, LFT’s and tumour markers as appropriate
Weekly FBC during treatment period
U&E’s and LFT’s every two weeks whilst on treatment

ASSESSMENT OF RESPONSE
Assessed radiologically after completion of radiotherapy.

REVIEW BY CLINICIAN
CAPECITABINE-Radiation-CNTW-protocol-CRP09-CR018 V1.3
Issue Date 29/05/2014
Page 1 of 4
Expiry Date May 2016
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Reviewed by either a Nurse, Pharmacist or Clinician during treatment.

ADMINISTRATION NOTES

Optimal timing of (capecitabine) with radiotherapy
There is conflicting evidence in the literature on the timing of administration of capecitabine in relation to the timing of radiotherapy and effect on clinical outcomes. It appears that timing is not critical but it would be sensible for capecitabine to be administered 1 to 2 hours prior to radiotherapy as capecitabine and its metabolites reach peak plasma concentrations 1 to 2 hours after a single oral administration.

Counselling Points for Oral Capecitabine

| How to take: | Take tablets 12 hours apart, within 30 minutes after the end of meal (i.e. breakfast & evening meal.) Swallow whole with water |
| Side effects | Common side effects to discuss with patient include; diarrhoea, nausea & vomiting, stomatitis (mouth ulcers), Hand-foot syndrome (painful red swelling in hands and feet), fever or infection. If patients notice any of these advise them to stop taking treatment, contact doctor/chemotherapy day unit who will take steps to manage side effects and advise on continuing treatment. |
| Missed dose: | If remember half an hour after they should have taken their tablets, then take the missed dose, otherwise only take the regular dose at next scheduled time. Do not double-up doses to make up for the missed doses or take extra doses at the end of the treatment cycle. |
| Post dose vomiting: | In the case of vomiting within a few hours after drug intake, never repeat the administration of the dose. |
| Storage/ Disposal | Tablets should be stored in cool dry place less than 30°C. Unused medicines must be returned to hospital pharmacy for disposal |

TOXICITIES
- Palmar/Plantar Erythrodysesthesia - Can be severe, patients must be forewarned
- Diarrhoea
- Abdominal pain
- Nausea and vomiting
- Pyrexia, fatique, asthenia, anorexia
- Myelosuppression
- Hyperbilirubinemia
- Stomatitis
- Contra-indicated in patients with severe hepatic impairment, a history of severe and unexpected reactions to fluoropyrimidine therapy, DPD deficiency, hypersensitivity. Avoid concomitant use with allopurinol
- Cardiotoxicity - Occasionally patients may experience coronary artery spasm.
- When combined with radiotherapy for rectal cancer, the Maximum Tolerated Dose (MTD) is 2000 mg/m² per day using either a continuous schedule or given daily Monday through Friday during a 6-week course of radiotherapy.

EXTRAVASATION NOT APPLICABLE ORAL THERAPY
DOSE MODIFICATION / TREATMENT DELAYS

Haematological Toxicity:
- ANC < 1-1.5 and/or platelets <100 delay capecitabine for 1 week but continue with radiotherapy. Repeat FBC if recovered restart with 25% dose reduction
- If further delays necessary consider further dose reduction (discuss with SpR/Consultant) or consider stopping treatment

*Note: Individual prescribers will make decision to treat based on blood counts within the flexible limits for NAC and platelets listed above. Check with prescriber before proceeding if ANC and platelets below the upper limits (ANC = 1.5, platelets = 100)

Non-Haematological Toxicity:
Patient should be given appropriate supportive care and managed as per table below

<table>
<thead>
<tr>
<th>Table of dose adjustments according to CTC toxicity (Not PPE/hand/foot)</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; appearance</td>
<td>Interrupt treatment until resolved to grade 0/1, then continue at 100% of original dose with prophylaxis where possible</td>
<td>Interrupt treatment until resolved to grade 0/1, then continue at 75% of original dose with prophylaxis where possible</td>
<td>Discontinue treatment</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; appearance</td>
<td>Interrupt treatment until resolved to grade 0/1, then continue at 75% of original dose</td>
<td>Interrupt treatment until resolved to grade0/1, then continue at 50% of original dose</td>
<td></td>
</tr>
<tr>
<td>3&lt;sup&gt;rd&lt;/sup&gt; appearance</td>
<td>Interrupt treatment until resolved to grade 0/1, then continue at 50% of original dose</td>
<td></td>
<td>Discontinue treatment</td>
</tr>
<tr>
<td>4&lt;sup&gt;th&lt;/sup&gt; appearance</td>
<td>Discontinue treatment</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Once the capecitabine dose has been reduced, it should **not** be increased at a later time. Omitted doses are **not replaced or restored**, instead the patient should resume the planned treatment cycle.

**Diarrhoea**
- Grade 2 during course of treatment - delay until recovered and give full dose
- Diarrhoea grade 3/4 during a course of treatment - delay until recovered and resume treatment at 25% reduced dose of capecitabine
- Note CTC grading for Diarrhoea toxicity grading
  - CTC Grade 1 = Diarrhoea (watery stool 2-3 times/day) **OR** mild increase in ostomy output compared to baseline
  - CTC Grade 2 = Diarrhoea (watery stool 4-6 times/day) **OR** moderate increase in ostomy output compared to baseline
  - CTC Grade 3/4 = Diarrhoea (watery stool >7 times/day **OR** severe increase in ostomy output compared to baseline

**Renal function:**
• Capecitabine is renally excreted; therefore dose requires adjustment for patients with moderate renal impairment (<50ml/min) require a 25% dose reduction.
• Contra-indicated in severe renal failure (CrCl <30ml/min) (Wright equation or measured GFR)

Table of hand/foot toxicity grading for capecitabine only

<table>
<thead>
<tr>
<th>Grade</th>
<th>Clinical</th>
<th>Functional</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Numbness, dysesthesia/parasthesia, tingling, painless swelling or erythema</td>
<td>Discomfort but no interruption Of normal activities</td>
</tr>
<tr>
<td>2</td>
<td>Painful erythema with swelling</td>
<td>Discomfort which affects activities of daily living</td>
</tr>
<tr>
<td>3</td>
<td>Moist desquamation, ulceration, Blistering, severe pain</td>
<td>Severe discomfort, unable to work or perform activities of daily living</td>
</tr>
</tbody>
</table>

TREATMENT LOCATION
Patient having radiotherapy at cancer centre, best practice is for regimen to be prescribed by clinical oncologist responsible for radiotherapy.

REFERENCES:

Document Control

<table>
<thead>
<tr>
<th>Document Title:</th>
<th>Capecitabine Radiation CNTW protocol</th>
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<tbody>
<tr>
<td>Document No:</td>
<td>CRP09 CR0013</td>
</tr>
<tr>
<td>Current Version:</td>
<td>1.2</td>
</tr>
<tr>
<td>Author:</td>
<td>Steve Williamson, Consultant Pharmacist</td>
</tr>
<tr>
<td>Approval Signature*:</td>
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<tr>
<td>Approved by:</td>
<td>Calum Polwart, Cancer Pharmacist Philip Atherton, Consultant Oncologist</td>
</tr>
<tr>
<td>Date Approved:</td>
<td>29/05/2014</td>
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<tr>
<td>Due for Review:</td>
<td>May 2016</td>
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<tr>
<td>Summary of Changes</td>
<td>1.1 Updated capecitabine dose/ toxicity modification advice</td>
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<tr>
<td></td>
<td>1.2 Protocol reviewed.</td>
</tr>
<tr>
<td></td>
<td>1.3 Protocol reviewed and reissued, Antiemetic advice updated</td>
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