Chemotherapy Protocol

COLORECTAL CANCER

CAPECITABINE and IRINOTECAN

(XELIRI)

Regimen

- Colorectal Cancer – Capecitabine-Irinotecan (XELIRI)

Indication

- Treatment of advanced colorectal cancer
- WHO Performance status 0, 1, 2
- Palliative intent

Toxicity

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adverse Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capecitabine</td>
<td>Palmar-plantar erythrodysesthesia, diarrhoea, mucositis, chest pain</td>
</tr>
<tr>
<td>Irinotecan</td>
<td>Acute cholinergic syndrome, diarrhoea (may be delayed), myelosuppression</td>
</tr>
</tbody>
</table>

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

Monitoring

Regimen

- FBC, U&E’s and LFT’s prior to each cycle
- Patients with complete or partial dihydropyrimidine dehydrogenase (DPD) deficiency are at increased risk of severe and fatal toxicity during treatment with capecitabine. All patients should be tested for DPD deficiency before initiation (cycle 1) to minimise the risk of these reactions.

Dose Modifications

The dose modifications listed are for haematological, liver and renal function only. Dose adjustments may be necessary for other toxicities as well.

In principle all dose reductions due to adverse drug reactions should not be re-escalated in subsequent cycles without consultant approval. It is also a general rule for chemotherapy that if a third dose reduction is necessary treatment should be stopped.
Please discuss all dose reductions / delays with the relevant consultant before prescribing if appropriate. The approach may be different depending on the clinical circumstances. The following is a general guide only.

Haematological

Consider blood transfusion if patient symptomatic of anaemia or has a haemoglobin of less than 8g/dL

If the neutrophils are less than $1.5 \times 10^9$/L and/or the platelets are less than $100 \times 10^9$/L then delay treatment for 7 days. If the counts recover at this time re-start the capecitabine at the original dose. The irinotecan dose should be reduced to 80% of the original dose. If a 14 day delay is required to allow counts to recover or there are two separate delays of 7 days during treatment consider reducing the dose of irinotecan to 50% of the original dose or stopping treatment.

This is one of the few regimens where asymptomatic low nadir neutrophil counts are an indication for dose modification. Where this figure is less than $0.5 \times 10^9$/L or where there has been an episode of febrile neutropenia the subsequent irinotecan dose should be reduced to 80% of the original dose.

Hepatic Impairment

<table>
<thead>
<tr>
<th>Drug</th>
<th>Billirubin $\mu$mol/L</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capecitabine</td>
<td>Lack of information available. In patients with mild to moderate hepatic dysfunction due to liver metastases, 100% dose is acceptable and monitor for toxicity</td>
<td></td>
</tr>
<tr>
<td>Irinotecan</td>
<td>less than 26</td>
<td>250mg/m²</td>
</tr>
<tr>
<td></td>
<td>26 - 51</td>
<td>200mg/m²</td>
</tr>
<tr>
<td></td>
<td>more than 51</td>
<td>Clinical decision</td>
</tr>
</tbody>
</table>

Renal Impairment

<table>
<thead>
<tr>
<th>Drug</th>
<th>Creatinine Clearance (ml/min)</th>
<th>Dose (% of original dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capecitabine</td>
<td>51 and above</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>30 - 50</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td>less than 30</td>
<td>Contra-indicated</td>
</tr>
<tr>
<td>Irinotecan</td>
<td>Dose reduction probably not required</td>
<td></td>
</tr>
</tbody>
</table>

Drug

Bilirubin $\mu$mol/L

Dose

Capecitabine

Lack of information available. In patients with mild to moderate hepatic dysfunction due to liver metastases, 100% dose is acceptable and monitor for toxicity

Irinotecan

less than 26

250mg/m²

26 - 51

200mg/m²

more than 51

Clinical decision

Renal Impairment

Drug

Creatinine Clearance (ml/min)

Dose (% of original dose)

Capecitabine

51 and above

100

30 - 50

75

less than 30

Contra-indicated

Irinotecan

Dose reduction probably not required
**Other Toxicities**

Dose reductions or interruptions in therapy are not necessary for those toxicities that are considered unlikely to be serious or life threatening. For example, alopecia, altered taste or nail changes. Dose limiting toxicities include diarrhoea, abdominal pain, emesis, stomatitis and palmar-planar erythrodysaesthesia among others. If chest pain occurs consider stopping capecitabine.

**Capecitabine**

**NCI-CTC Grade 2**

Interrupt treatment until the toxicity resolves to NCI-CTC grade 0-1 then continue at the same dose. If the toxicity recurs for a second time again interrupt treatment until it resolves to NCI-CTC grade 0-1 then resume therapy at 75% of the original dose. If the same adverse effect develops on a third occasion once more interrupt treatment until it resolves to NCI-CTC grade 0-1 then continue at 50% of the original dose. Stop treatment if the toxicity re-appears on a fourth instance.

**NCI-CTC Grade 3**

Interrupt treatment until the toxicity resolves to NCI-CTC grade 0-1 then continue treatment using 75% of the original dose with prophylaxis if appropriate. If the toxicity recurs for a second time again interrupt treatment until it resolves to NCI-CTC grade 0-1 and then resume therapy at 50% of the original dose. If the same adverse effect develops on a third occasion discontinue capecitabine.

**NCI-CTC Grade 4**

Discontinue treatment unless the responsible consultant considers it to be in the best interest of the patient to continue at 50% of the original dose once the toxicity has resolved to grade 0-1.

When capecitabine is stopped for toxicity the doses are omitted, not delayed.

**Irinotecan**

Irinotecan is associated with a number of toxic reactions. The next cycle of treatment should not be administered until all toxicities have resolved to NCI-CTC 0 or 1. Diarrhoea must have resolved completely. Where a NCI-CTC grade 3 or above event has occurred the irinotecan dose must be reduced to 80% of the original dose.

**Regimen**

**21 day cycle for 4 cycles**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Days</th>
<th>Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capecitabine</td>
<td>1000mg/m² twice a day</td>
<td>1 – 14 inclusive</td>
<td>Oral</td>
</tr>
<tr>
<td>Irinotecan</td>
<td>250mg/m²²</td>
<td>1</td>
<td>Intravenous infusion in 250ml sodium chloride 0.9% over 90 minutes</td>
</tr>
</tbody>
</table>
In those individuals who have had prior radical radiotherapy to the pelvis or who are 70 years of age and above or who have a performance status of 2 consider starting therapy with attenuated doses.

**Dose Information**

- Capecitabine will be dose banded in accordance with the national dose bands
- Irinotecan will be dose banded in accordance with the national dose bands (20mg/ml)
- The maximum dose of irinotecan is 700mg.

**Administration Information**

**Extravasation**

- Irinotecan – irritant

**Other**

- Capecitabine should start on the evening of day 1
- Capecitabine should be taken with or after food
- Irinotecan can be administered over 30-90 minutes

**Additional Therapy**

- Antiemetics
  
  15-30 minutes prior to chemotherapy on *day one* only
  
  - dexamethasone 8mg oral or intravenous
  - ondansetron 8mg oral or intravenous

  As take home medication;

  - dexamethasone 4mg twice a day for 3 days oral
  - metoclopramide 10mg three times a day when required

- Subcutaneous atropine 250microgram immediately prior to irinotecan for the prevention of acute cholinergic syndrome. A further 250microgram subcutaneous dose may be given to relieve cholinergic symptoms if they develop.

- Oral loperamide 2mg every two hours once first liquid stool appears and continue until 12 hours after the last liquid stool. Do not use for longer than 48 hours.
• Consider oral ciprofloxacin 500mg twice daily where diarrhoea continues for more than 24 hours. Review the patient before starting this treatment.

• Mouthwashes according to local policy on the treatment of mucositis

• Gastric protection with a proton pump inhibitor or a H₂ antagonist may be considered in patients considered at high risk of GI ulceration or bleed.

Additional information

• The National Patient Safety Agency alert NPSA/2008/RRR001 must be followed when prescribing, dispensing or administering oral chemotherapy.

• Ensure the total daily dose of capecitabine is divided into two doses given twelve hours apart (the first should be administered in the evening of day one of the cycle) Serious toxicity has occurred where the total daily dose has been given twice a day.

• It must be made clear to all staff, including those in the community, that this is a short course of oral chemotherapy that must not be continued.

References
REGIMEN SUMMARY

Day 1

1. Atropine 250mcg subcutaneous
2. Dexamethasone 8mg oral or intravenous
3. Ondansetron 8mg oral or intravenous
4. Irinotecan 250mg/m\(^2\) intravenous infusion in 250ml sodium chloride 0.9% over 90 minutes
5. Atropine 250mcg subcutaneous when required for the relief of cholinergic symptoms

Take Home Medicines

6. Capecitabine 1000mg/m\(^2\) twice a day for 14 days oral
7. Dexamethasone 4mg twice a day for 3 days oral starting the day after irinotecan
8. Metoclopramide 10mg three times a day when required oral
This chemotherapy protocol has been developed as part of the chemotherapy electronic prescribing project. This was and remains a collaborative project that originated from the former CSCCN. These documents have been approved on behalf of the following Trusts:

Hampshire Hospitals NHS Foundation Trust  
NHS Isle of Wight  
Portsmouth Hospitals NHS Trust  
Salisbury NHS Foundation Trust  
University Hospital Southampton NHS Foundation Trust  
Western Sussex Hospitals NHS Foundation Trust

All actions have been taken to ensure these protocols are correct. However, no responsibility can be taken for errors which occur as a result of following these guidelines.