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

Drug	Adverse Effect
Capecitabine	Palmar-plantar erythrodysesthesia, diarrhoea, mucositis, chest pain
Irinotecan	Acute cholinergic syndrome, diarrhoea (may be delayed), myelosuppression

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 $1.5x10^9$/L and/or the platelets are less than $100x10^9$/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 $0.5x10^9$/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

Drug	Bilirubin µmol/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/m^2
	26 - 51	200mg/m^2
	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-plantar erythrodysesthesia 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

Drug	Dose	Days	Administration
Capecitabine	1000mg/m2 twice a day	1 – 14 inclusive	Oral
Irinotecan	250mg/m^2	1	Intravenous infusion in 250ml sodium chloride 0.9% over 90 minutes

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 H_2 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
1. Fuchs C, Marshall J, Barrueco J et al. Randomised controlled trial of irinotecan plus infusional, bolus or oral fluoropyrimidines in first line treatment of metastatic colorectal cancer. Updated results from the BICC-C study. J Clin Oncol 2008; 26 (4): 689-690.
2. Choi CK, Chan RT, Tung SY et al. Efficacy of combination chemotherapy with irinotecan (CPT-11) and capecitabine in patients with metastatic or advanced colorectal carcinoma – a dual centre phase II study – the MAC 6. Clin Oncol (R Coll Radiol) 2008; 20 (2): 168-175.
3. Gennatas C, Michalaki V, Gennatas S et al. Irinotecan and capecitabine as first line therapy in advanced colorectal cancer. Anticancer Research 2008; 28 (3B): 1923-1926.
4. National Institute for Health and Clinical Excellence. Technology Appraisal 93. Colorectal cancer (advanced). Irinotecan, oxaliplatin and raltitrexed (review). DOH: London
5. Patt YZ, Lee FC. Liebmann JE et al. Capecitabine plus three weekly irinotecan (XELIRI) as first line chemotherapy for metastatic colorectal cancer: phase II trial results. J Clin Oncol 2007; 30 (4): 350-357.

REGIMEN SUMMARY

Day 1

1. Atropine 250mcg subcutaneous

2. Dexamethasone 8mg oral or intravenous

3. Ondansetron 8mg oral or intrevenous

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

DOCUMENT CONTROL

Version	Date	Amendment	Written/ Amended By	Approved By
1.3	Nov 2020	Updated monitoring with DPD testing Dose banding statement updated Coding removed	Donna Kimber Pharmacy Technician	Rebecca Wills Pharmacist
1.2	May 2014	Header changed Metoclopramide dose changed to 10mg Intravenous added to ondansetron and dexamethasone OPCS updated Atropine dose added Dexamethasone TTO clarified Disclaimer added	Dr Debbie Wright Pharmacist	Donna Kimber Pharmacy Technician
1.1	Jan 2013	Document control table added. Duration if infusion of irinotecan changed from 30 minutes to 90 minutes in the regimen and regimen summary. OPCS procurement code changed from X70.5 to X70.4. OPCS delivery code changed from X72.3 to X72.2. Adverse effects tabulated Liver / kidney impairment recommendation tabulated Dose table tabulated Atropine dose changed to 250mcg. Antiemetics changed to oral. Twice daily changed to twice a day. Mouthwashes changed	Rebecca Wills Pharmacist	Dr Debbie Wright Pharmacist
1	August 2010	None	Dr Debbie Wright Pharmacist	Dr Tim Iveson Consultant Medical Oncologist

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.