Chemotherapy Protocol

COLORECTAL CANCER

CAPECITABINE and OXALIPLATIN

(CAPOX)

Regimen

- Colorectal Cancer – Capecitabine-Oxaliplatin (CAPOX)

Indication

- Advanced / metastatic colorectal cancer
- Adjuvant therapy of stage III colon cancer following surgery
- WHO performance status 0, 1, 2

Toxicity

Drug	Adverse Effect
Capecitabine	Palmar-plantar erythrodysesthesia, diarrhoea, mucositis, chest pain
Oxaliplatin	Peripheral neuropathy (cumulative), acute laryngopharyngeal dysasthesia (increase duration of infusion)

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

Monitoring

Regimen

- FBC, LFT's and U&E'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

Prior to prescribing the following criteria must be met;

Criteria	Eligible Level
Neutrophils	Equal to or more than $1.5x10^9$/L
Platelets	Equal to or more than $100x10^9$/L

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

For haematological toxicity, if the neutrophil count is less than 1.5×10^9/L or the platelet count is less than 75×10^9/L, delay treatment until these levels are achieved. Re-initiate therapy at the full dose for a 7 day delay or with 75% of the original dose for a 14 day delay (consider re-starting with 100%). If the delay is ≥ 21 days stop therapy.

Hepatic Impairment

Drug	Bilirubin (µmol/L)		AST/ALT	Dose (% of original dose)
Capecitabine	greater than 3xULN	or	greater than 2.5xULN	If treatment related consider delaying treatment. For mild/moderate hepatic dysfunction due to liver metastasis dose modification may not be necessary.
Oxaliplatin	n/a		n/a	No dose adjustment necessary

Renal Impairment

Drug	Creatinine Clearance (ml/min)	Dose (% of original dose)
Capecitabine	51 or greater	100%
	30-50	75%
	less than 30	Contra-indicated
Oxaliplatin	30 or greater	Dose adjust according to toxicity
	less than 30	Avoid

Other

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, palmar-plantar erythrodysesthesia and neurosensory toxicities among others. If chest pain occurs consider stopping capecitabine.

If any NCI-CTC grade 1 toxicity occurs treatment should be continued, without interruption, at the full dose.

For toxicities of NCI-CTC grade 3 treatment should be withheld until recovery to NCI-CTC grade 1 or below then re-started if medically appropriate. If recovery takes 21 days or longer then stop treatment.

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 NCI-CTC grade 0-1.

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

Oxaliplatin

For cold related dysaesthesia or paresthesia with out pain there is no need to dose delay or reduce unless it persists between cycles. In this instance withhold the oxaliplatin until recovery and then re-start treatment using 100mg/m^2. Only omit the oxaliplatin if it recurs.

For paresthesiae with pain or functional impairment that lasts 7 days or less no dose modification is necessary. If it persists beyond 7 days or is NCI-CTC grade 3 and above, in the first instance reduce the dose to 100mg/m^2. If the painful paresthesia recurs or persists between cycles omit the oxaliplatin.

If NCI-CTC grade 3-4 diarrhoea or stomatitis recurs despite appropriate reduction in the capecitabine dose the oxaliplatin dose should be reduced to 100mg/m^2.

There are rare case reports of acute interstitial lung disease or lung fibrosis in association with oxaliplatin. Where an unexplained respiratory symptom occurs stop treatment until pulmonary investigations have been conducted to exclude an interstitial cause.

Regimen

21 day cycle for 8 cycles

Patients with metastatic disease should normally be assessed for response to treatment after 4 cycles. If the disease is stable or has responded a further 4 cycles of therapy may be given after which response should once again be determined.

Drug	Dose	Days	Administration
Capecitabine	1000mg/m^2 twice a day	1-14	Oral
Oxaliplatin	130mg/m^2	1	Intravenous infusion in 500ml glucose 5% over 120 minutes

For those aged 70 years and above consider starting treatment using the following dose modifications for capecitabine only.

Drug	Dose	Days	Administration
Capecitabine	800mg/m^2 twice a day	1-14	Oral
Oxaliplatin	130mg/m^2	1	Intravenous infusion in 500ml glucose 5% over 120 minutes

Dose Information

- Capecitabine will be dose banded in accordance with the national dose bands
- Oxaliplatin will be dose banded in accordance with the national dose bands (5mg/ml)

Administration Information

Extravasation

- Oxaliplatin – exfoliant

Other

- Capecitabine should start on the evening of day 1.
- Capecitabine should be taken with or after food.

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

- Oral loperamide 4mg after the first loose stool then 2-4mg four times a day when required for the relief of diarrhoea (maximum 16mg/24 hours).

- Mouthwash according to local or national guidelines

- 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. Cassidy J, Tabernero J, Twelves C et al. XELOX (capecitabine plus oxaliplatin): Active first line therapy for patients with metastatic colorectal cancer. J Clin Oncol 2004; 22 (11): 2084-2091.
2. Scheithauer W, Kornek GV, Raderer M et al. Randomised multicentre phase II trial of two different schedules of capecitabine plus oxaliplatin as first line treatment in advanced colorectal cancer. J Clin Oncol 2003; 21 (7): 1307-12.
3. Borner M, Dietrick D, Stupp R et al. Phase II study of capecitabine and oxaliplatin in first and second line treatment of advanced or metastatic colorectal cancer. J Clin Oncol 2002;20 (7): 1759-66.

REGIMEN SUMMARY

Capecitabine-Oxaliplatin (CAPOX)

Day One

1. Dexamethasone 8mg oral or intravenous

2. Ondansetron 8mg oral or intravenous

3. Oxaliplatin 130mg/m^2 intravenous infusion in 500ml glucose 5% over 120 minutes

Take Home Medicines

4. Capecitabine 1000mg/m^2 twice a day for 14 days oral

5. Dexamethasone 4mg twice a day for 3 days oral starting the day after oxaliplatin

6. Metoclopramide 10mg three times a day when required oral

DOCUMENT CONTROL

Version	Date	Amendment	Written 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 Tabulation throughout < or > symbols written out in full. NCI-CTC added to toxicity grades Bolus removed from intravenous bolus Stat removed Treatment of mucositis changed Pyridoxine removed Metoclopramide dose changed to 10mg throughout Dexamethasone TTO clarified Disclaimer added	Dr Deborah Wright Pharmacist	Donna Kimber Pharmacy Technician
1.1	Jan 2011	Oxaliplatin changed to be diluted in 500ml glucose 5%	Dr Deborah Wright Pharmacist	Donna Kimber Pharmacy Technician
1	Aug 2010	None	Dr Deborah 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.