Chemotherapy Protocol

COLORECTAL CANCER

BEVACIZUMAB-CAPECITABINE-OXALIPLATIN

This protocol may require funding

Regimen

- Colorectal Cancer– Bevacizumab-Capecitabine-Oxaliplatin

Indication

- Metastatic colorectal cancer
- WHO performance status 0, 1

Toxicity

Drug	Adverse Effect
Bevacizumab	Haemorrhage, hypertension, proteinuria, impaired wound healing, gastrointestinal perforations, fistulae, arterial thrombosis
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

Drugs

- FBC, LFTs and U&Es prior to day one of treatment
- Blood pressure and dipstick urinalysis for proteinuria prior to treatment with bevacizumab
- 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 and some drug specific toxicities 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. (See below for information on bevacizumab and transfusions).

Prior to prescribing on day one of cycle one 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

Dose modifications for haematological toxicity apply to capecitabine and oxaliplatin only.

Neutrophils ($x10^9$/L)	**Dose Modifications (capecitabine and oxaliplatin)**
1.5 or greater	100%
less than 1.5	Delay until neutrophils recover to $1.5x10^9$/L or greater. If recovery occurs within 7 days restart at 100% of the original dose. If recovery occurs within 7-14 days restart at 75% (100% where appropriate) of the original dose. If recovery takes greater than 21 days stop treatment.
Platelets ($x10^9$/L)	**Dose Modifications (capecitabine and oxaliplatin)**
75 or greater	100%
less than 75	Delay until platelets recover to $75x10^9$/L or greater. If recovery occurs within 7 days restart at 100% of the original dose. If recovery occurs within 7-14 days restart at 75% (100% where appropriate) of the original dose. If recovery takes greater than 21 days stop treatment.

There is little need to adjust the dose of bevacizumab for haematological toxicity.

Hepatic Impairment

Please note that the approach may be different where abnormal liver function tests are due to disease involvement.

Drug	Bilirubin (µmol/L)		AST/ALT	Dose (% of original dose)
Bevacizumab	n/a		n/a	No information available
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)
Bevacizumab	n/a	No information available
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.

Bevacizumab

Bevacizumab doses should be omitted and not reduced for adverse reactions. If more than two doses are missed due to adverse events treatment should be stopped. It should be noted that the half life of bevacizumab is approximately twenty days. Discontinuation of treatment in response to adverse effects is not expected to influence the short term clinical evolution of the event, symptomatic treatment is often necessary.

Bevacizumab should be stopped if the individual develops;

- Gastrointestinal perforation
- Arterial thromboembolic events
- NCI-CTC grade 3 and above haemorrhagic events (requiring a blood transfusion or a major non-elective intervention)
- NCI-CTC grade 3 and above congestive heart failure or left ventricular function
- NCI-CTC grade 4 fistula

If a NCI-CTC symptomatic grade 4 venous thromboembolic event occurs bevacizumab should be stopped. However, if this is a pulmonary embolism bevacizumab may be re-started once a full recovery has been made and the individual is anti-coagulated with a subcutaneous low molecular weight heparin. An oral anticoagulant must not be used.

Hypertension is a common consequence of bevacizumab therapy. For a NCI-CTC grade 1 hypertension no treatment is necessary. NCI-CTC grade 2 hypertension, consider anti-hypertensive therapy. For a NCI-CTC grade 3 and above hypertension that is persistent consider stopping treatment.

Bevacizumab may be continued for a NCI-CTC grade 1 proteinuria or the first occurrence of a grade 2 proteinuria. For the second occurrence of a NCI-CTC grade 2 proteinuria or any NCI-CTC grade 3 proteinuria give the bevacizumab as scheduled. A 24 hour urine collection or UPCR should be conducted at most three days before the next dose. If there is less than 2g protein per 24 hours or a UPCR 0-1 administer the bevacizumab and return to dipstick monitoring. If there is more than 2g protein per 24 hours omit the bevacizumab. Repeat the 24 hour urine collection prior to the next scheduled dose. If this is less than 2g per 24 hours administer the bevacizumab and continue 24 hour urine collection until the protein is 1g per 24 hours or less.

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 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 without 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 6 cycles

Drug	Dose	Days	Administration
Bevacizumab	7.5mg/kg	1	Intravenous infusion in 100ml sodium chloride 0.9% over 90 minutes (see administration information)
Capecitabine	1000mg/m^2 twice a day	1-14	Oral
Oxaliplatin	130mg/m^2	1	Intravenous infusion in 500ml glucose 5% over 120 minutes

If continuing treatment beyond six cycles consider stopping oxaliplatin from cycle 7 onwards to minimise the risk of serious peripheral sensory neuropathy. If oxaliplatin is stopped the dose of capecitabine may be increased at this point to 1250mg/m^2 twice a day if clinically appropriate.

Dose Information

- Bevacizumab will be dose banded in accordance with the national dose bands (25mg/ml NS)
- In patients over 70 years old consider initiating capecitabine treatment at 800mg/m^2 twice a day.
- 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

- Bevacizumab - neutral
- Oxaliplatin - exfoliant

Other

- The first infusion of bevacizumab will be over 90 minutes. If this is well tolerated the second infusion may be given over 60 minutes. If this is well tolerated subsequent infusions may be given over 30 minutes
- Capecitabine should start on the evening of day 1
- Capecitabine should be taken with or after food
- A glucose 5% flush should be administered before and after the oxaliplatin

Additional Therapy

- Antiemetics

  15-30 minutes prior to chemotherapy

  - ondansetron 8mg oral or intravenous
  - dexamethasone 8mg oral or equivalent intravenous dose

  As take home medication

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

- Oral loperamide 4mg initially then 2mg after each loose stool when required for the relief of diarrhoea (maximum 16mg/24 hours).
- Mouthcare for the prophylaxis or treatment of mucositis in accordance with 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. Diaz-Rubio E, Gomez-Espana A, Massuti B et al. First line XELOX plus bevacizumab followed by XELOX plus bevacizumab or single agent bevacizumab as maintenance therapy in patients with metastatic colorectal cancer: The phase III MACRO TTD study. The Oncologist 2012; 17 (1): 15-25.

REGIMEN SUMMARY

Bevacizumab-Capecitabine-Oxaliplatin

Day 1

1. Dexamethasone 8mg oral or intravenous

2. Ondansetron 8mg oral or intravenous

3. Bevacizumab 7.5mg/kg intravenous infusion in 100ml sodium chloride 0.9% over 90 minutes

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

Take home medicines

5. Capecitabine 1000mg/m^2 oral twice a day for 14 days starting on the evening of day one of the cycle

6. Dexamethasone 4mg oral twice a day for 3 days starting the day after chemotherapy administration

7. Metoclopramide 10mg oral three times a day for 3 days then when required for the relief of nausea.

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1.2	Nov 2020	Updated monitoring with DPD testing Dose banding statement updated Coding removed	Donna Kimber Pharmacy Technician	Rebecca Wills Pharmacist
1.1	May 2014	Header changed < symbol removed from paragraph on dose modifications Capecitabine dose modifications for age moved to section on "dose modifications" Bolus removed from intravenous bolus Metoclopramide dose changed to 10mg throughout Dexamethasone and capecitabine administration clarified Coding updated Intravenous added to antiemetics in summary Disclaimer added	Dr Deborah Wright Pharmacist	Donna Kimber Pharmacy Technician
1	Feb 2013	None	Rebecca Wills Pharmacist 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.