Chemotherapy Protocol

COLORECTAL CANCER

BEVACIZUMAB-FLUOROURACIL-FOLINIC ACID (Modified de Gramont)-OXALIPLATIN

This regimen may require funding

Regimen

- Colorectal Cancer – Bevacizumab-Fluorouracil-Folinic Acid (modified de Gramont)-Oxaliplatin

Indication

- Bevacizumab in combination with a fluoropyrimidine and oxaliplatin chemotherapy is indicated as a possible first, second or third line treatment for metastatic colorectal cancer (please refer to the current list of CDF indications for further details. This can be accessed at http://www.england.nhs.uk/wp-content/uploads/2014/03/ncdf-list-mar14.pdf).

- WHO performance status 0, 1

Toxicity

Drug	Adverse Effect
Bevacizumab	Haemorrhage, hypertension, proteinuria, impaired wound healing, gastrointestinal perforations, fistulae, arterial thrombosis
Fluorouracil	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, LFT's and U&E's 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 fluorouracil. 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 on day one of cycle one the following criteria must be met;

Criteria	Eligible Level
Neutrophil	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 (see below for information on bevacizumab and transfusions).

For haematological toxicity, if the neutrophil count is less than 1.5×10^9/L or the platelet count less than 75×10^9/L, delay treatment until these levels are achieved. Reinitiate therapy at the full dose for up to a seven day delay or, for a delay of more than seven days, with 75% of the original dose for thrombocytopenia. If neutropenia is the issue after seven days omit the bolus fluorouracil for this and subsequent cycles. If a further delay is necessary despite omitting the bolus fluorouracil then reduce the dose of both the infusional fluorouracil and oxaliplatin to 80% of the original dose. If the delay is twenty-one days or longer days stop therapy.

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

Hepatic / Renal Impairment

Deteriorating liver or kidney function may be a sign of disease progression or drug toxicity.

Drug	Hepatic	Renal
Bevacizumab	No information available	No information available
Fluorouracil	If the bilirubin is more than 85umol/L and / or the AST more than 180 fluorouracil is contra-indicated. In moderate hepatic impairment consider reducing the dose by 30%	A dose adjustment is only required in severe renal impairment

	and for severe impairment by 50%	
Oxaliplatin	No adjustments necessary	Consider dose adjustment according to toxicity Avoid when the CrCl is less than 30ml/min

Other

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 NCI-CTC 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.

Fluorouracil

Diarrhoea occurring for the first time at NCI-CTC grade 2 should be approached by withholding the fluorouracil until it has resolved to NCI-CTC grade 1 or below. Treatment can then be re-started at full dose. Treatment should again be delayed on development of a second NCI-CTC grade 2 diarrhoea and the fluorouracil re-started at 75% of the original dose when it has resolved to NCI-CTC grade 1 or below. After resolution of a third episode of NCI-CTC grade 2 diarrhoea to NCI-CTC grade 1 or below, the fluorouracil should be re-started using 50% of the original dose.

On appearance of a NCI-CTC grade 3 diarrhoea withhold fluorouracil until it has resolved to NCI-CTC grade 1 or below and re-start treatment using 75% of the original dose. After a second episode at NCI-CTC grade 3 wait until the diarrhoea has resolved to NCI-CTC grade 1 or below and resume the fluorouracil using 50% of the original dose. For a third appearance of NCI-CTC grade 3 diarrhoea or the development of NCI-CTC grade 4 toxicity at any time stop fluorouracil therapy.

Oxaliplatin

If the neurosensory toxicity is NCI-CTC grade 1–2 and lasts less than seven days administer full dose oxaliplatin. If the toxicity is NCI-CTC grade 2 and persists for more than seven days reduce the oxaliplatin dose to 75mg/m^2. Oxaliplatin should be discontinued for neurosensory toxicities NCI-CTC grade 3 or above.

If NCI-CTC grade 3-4 diarrhoea or stomatitis recurs despite appropriate reduction in the fluorouracil dose the oxaliplatin dose should be reduced to 75mg/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.

Regimen

14 day cycle for 6 cycles

Drug	Dose	Days	Route
Bevacizumab	5mg/kg	1	Intravenous infusion in 100ml sodium chloride 0.9% over 90 minutes (see administration information)
Fluorouracil	400mg/m^2	1	Intravenous bolus over 10 minutes
Fluorouracil	2400mg/m^2	1	Intravenous infusion over 46 hours
Folinic Acid	350mg	1	Intravenous infusion in 250ml glucose 5% over 120 minutes
Oxaliplatin	85mg/m^2	1	Intravenous infusion in 500ml glucose 5% over 120 minutes

Dose Information

- Bevacizumab will be dose banded in accordance with the national dose bands (25mg/ml NS)
- Fluorouracil will be dose banded in accordance with the national dose bands (25mg/ml PM bolus and 50mg/ml infusion)

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

Administration Information

Extravasation

- Bevacizumab - neutral
- Fluorouracil – inflammitant
- Oxaliplatin - exfoliant

Other

- Central venous access and use of an ambulatory infusion pump is required
- 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
- A glucose 5% flush should be administered before and after the oxaliplatin

Additional Therapy

- Antiemetics

  15-30 minutes prior to chemotherapy

  - 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

- 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
- 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).

Additional Information

- The folinic acid may be replaced with calcium levofolinate 175mg intravenous infusion in 250ml glucose 5% over 120 minutes

References

1. Giantonio BJ, Catalano PJ, Meropol NJ et al. Bevacizumab in combination with oxaliplatin, fluorouracil and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: results from the Easter Co-operative Oncology Group Study E3200. J Clin Oncol 2007; 25 (12): 1539-1544.

REGIMEN SUMMARY

Bevacizumab-Fluorouracil-Folinic Acid (MdG)-Oxaliplatin

Day One

1. Dexamethasone 8mg oral or intravenous

2. Ondansetron 8mg oral or intravenous

3. Bevacizumab 5mg/kg in 100ml sodium chloride 0.9% over 90 minutes intravenous infusion*

4. Oxaliplatin 85mg/m^2 in 500ml glucose 5% over 120 minutes intravenous infusion

5. Folinic Acid 350mg in 250ml glucose 5% over 120 minutes intravenous infusion

6. Fluorouracil 400mg/m^2 over 10 minutes intravenous bolus

7. Fluorouracil 2400mg/m^2 over 46 hours intravenous infusion

Take Home Medicines

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

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

*Please refer to the administration instructions in Aria for details of bevacizumab infusion rates

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1.4	Nov 2020	Updated monitoring with DPD testing Dose banding updated Coding removed	Donna Kimber Pharmacy Technician	Rebecca Wills Pharmacist
1.3	May 2014	Header changed Indications updated with reference to the CDF Toxicities removed Coding updated Bolus removed from antiemetics Metoclopramide dose changed to 10mg Coding updated Time of bevacizumab administration changed to 90 minutes Dexamethasone TTO clarified Disclaimer added	Dr Debbie Wright Pharmacist	Donna Kimber Pharmacy Technician
1.2	June 2012	Oxaliplatin name added to drug column in hepatic / renal table	Dr Debbie Wright Pharmacist	Donna Kimber Pharmacy Technician
1.1	May 2012	Fluorouracil bolus administration time changed to 10 minutes Metoclopramide instructions changed on take home medicines	Dr Debbie Wright Pharmacist	Debra Robertson Pharmacist
1	March 2012	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.