Chemotherapy Protocol

COLORECTAL CANCER

BEVACIZUMAB-IRINOTECAN

This protocol may require funding

Regimen

- Colorectal Cancer – Bevacizumab-Irinotecan

Indication

- First line treatment of metastatic or advanced colorectal cancer in patients unsuitable for fluoropyrimidines who have not had prior bevacizumab therapy
- WHO performance status 0, 1

Toxicity

Drug	Adverse Effect
Bevacizumab	Haemorrhage, hypertension, proteinuria, impaired wound healing, gastrointestinal perforations, fistulae, arterial thrombosis
Irinotecan	Acute cholinergic syndrome, diarrhoea (may be delayed)

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

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

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

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).

Please note this is one of the few regimens where asymptomatic low nadir neutrophil counts are an indication for dose modification.

Dose modifications for haematological toxicity apply to irinotecan only.

Neutrophils ($x10^9$/L)	Dose Modifications (irinotecan)
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 80% of the original dose. If recovery occurs within 7-14 days or repeated delays are necessary consider reducing the dose to 50% of the original dose or stopping treatment.
Nadir less than 0.5 or febrile neutropenia	Delay until recovery then continue with 80% of the original dose,
Platelets ($x10^9$/L)	**Dose Modifications (irinotecan)**
100 or greater	100%
less than 100	Delay until platelets recover to $100x10^9$/L or greater. If recovery occurs within 7 days restart treatment at 80% of the original dose. If recovery occurs within 7-14 days or repeated delays are necessary consider reducing the dose 50% of the original dose or stopping 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
Irinotecan	26-51		n/a	200mg/m^2
	greater than 51		n/a	Clinical decision

Renal Impairment

Drug	Creatinine Clearance (ml/min)	Dose (% of original dose)
Bevacizumab	n/a	No information available
Irinotecan	n/a	No dose adjustment necessary

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.

Irinotecan

Dose limiting toxicities include diarrhoea, abdominal pain, emesis and stomatitis among others.

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 grade 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 8 cycles

Drug	Dose	Days	Administration
Bevacizumab	7.5mg/kg	1	Intravenous infusion in 100ml sodium chloride 0.9% over 90 minutes (see administration information)
Irinotecan	350mg/m^2	1	Intravenous infusion in 250ml sodium chloride 0.9% over 90 minutes

Dose Information

- Bevacizumab will be dose banded according to the CSCCN agreed bands
- 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 using irinotecan 300mg/m^2 (maximum dose 600mg).
- Irinotecan will be dose banded according to the CSCCN agreed bands
- The maximum single dose of irinotecan is 700mg

Administration Information

Extravasation

- Bevacizumab - neutral

- Irinotecan - irritant

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

- Irinotecan may be given over 30-90 minutes

Additional Therapy

- Antiemetics

  15-30 minutes prior to chemotherapy

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

  As take home medication

  - dexamethasone 4mg oral twice a day for 3 days
  - metoclopramide 10mg oral three times a day for 3 days then 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 (maximum daily dose is 16mg). Please refer to the CSCCN guidelines on treatment of irinotecan related diarrhoea Consider oral ciprofloxacin 500mg twice daily where diarrhoea continues for more than 24 hours. Review the patient before starting this treatment. Please refer to the CSCCN guidelines on treatment of irinotecan related diarrhoea.

- 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.

Coding (OPCS 4.6)

- Procurement – X71.5

- Delivery – X72.1

References
1. Macedo LT, da Costa Lima AB, Sasse AD et al. Addition of bevacizumab to first line chemotherapy in advanced colorectal cancer: a systematic review and meta-analysis with emphasis on chemotherapy subgroups. BMC Cancer 2012; 12 (89); 1471 2407.

REGIMEN SUMMARY

Bevacizumab-Irinotecan

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. Atropine 250micrograms subcutaneous
5. Irinotecan 350mg/m^2 intravenous infusion in 250ml sodium chloride 0.9% over 90 minutes
6. Atropine Sulphate 250mcg subcutaneous when required for the relief of cholinergic symptoms.

Take home medicines

7. Dexamethasone 4mg oral twice a day for 3 days starting the day after chemotherapy administration
8. Metoclopramide 10mg oral three times a day for 3 days then 10mg three times a day when required for the relief of nausea.

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1.1	April 2014	Header changed Bolus removed from intravenous bolus throughout text Paragraph on dose adjustments moved from under “regimen” to be under “dose information” Metoclopramide dose changed to 10mg OPCS codes updated Atropine added as pre-treatment to irinotecan Dexamethasone TTO clarified 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 Hospital 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.