Chemotherapy Protocol

COLORECTAL CANCER

AFLIBERCEPT-FLUOROURACIL-FOLINIC ACID (Modified de Gramont)-IRINOTECAN

This regimen may require funding

Regimen

- Colorectal Cancer – Aflibercept-Fluorouracil-Folinic Acid (modified de Gramont)-Irinotecan

Indication

- Aflibercept in combination with a fluoropyrimidine and irinotecan chemotherapy is indicated as second line treatment for metastatic colorectal cancer following progression after first line treatment with an oxaliplatin based regimen with or with out bevacizumab

- WHO performance status 0, 1

Toxicity

Drug	Adverse Effect
Aflibercept	Haemorrhage, hypertension, proteinuria, impaired wound healing, gastrointestinal perforations, fistulae, arterial thrombosis, posterior reversible encephalopathy syndrome
Fluorouracil	Palmar-plantar erythrodysesthesia, diarrhoea, mucositis, chest pain
Irinotecan	Acute cholinergic syndrome, diarrhoea (may be delayed)

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 aflibercept

- 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).

If the neutrophils are less than $1.5x10^9$/L and/or the platelets are less than $100x10^9$/L then delay treatment for seven days. If the counts recover at this time omit the bolus fluorouracil and consider restarting the irinotecan at 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 and fluorouracil dose should be reduced to 80% of the original dose and consider stopping the bolus fluorouracil.

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

Hepatic Impairment

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

Drug	Bilirubin (µmol/L)		AST/ALT units	Dose
Aflibercept	less than 3xULN		n/a	No dose adjustment is required although formal studies are lacking.

Fluorouracil	More than 85		More than 180	Contra-indicated. In moderate hepatic impairment consider reducing the dose by 30% and for severe impairment by 50%
Irinotecan	More than 3xULN		n/a	Contra-indicated.

Renal Impairment

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

Drug	Creatinine Clearance (ml/min)	Dose (% of original dose)
Aflibercept	More than 30	No dose adjustment required although formal studies are lacking
Fluorouracil	n/a	Dose adjustment is only required in severe renal impairment
Irinotecan		Limited information.

Other

Aflibercept

Aflibercept 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.

Aflibercept 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
- Posterior reversible encephalopathy syndrome

If a NCI-CTC symptomatic grade 4 venous thromboembolic event occurs aflibercept should be stopped. However, if this is a pulmonary embolism aflibercept 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 aflibercept therapy. Pre-existing hypertension must be controlled prior to starting treatment. For a NCI-CTC grade 1 hypertension no treatment is necessary. NCI-CTC grade 2 hypertension, consider anti-hypertensive therapy such as an ACEI. For a NCI-CTC grade 3 and above

hypertension that is persistent stop treatment until it is controlled and then either dose reduce to 2mg/kg or stop treatment. Aflibercept should be stopped for uncontrolled hypertension, a hypertensive crisis or if a hypertensive encephalopathy develops.

Aflibercept 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 aflibercept 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 aflibercept and return to dipstick monitoring. If there is more than 2g protein per 24 hours omit the aflibercept until the protein is less than 2g per 24 hours. Repeat the 24 hour urine collection prior to the next scheduled dose. If this is less than 2g per 24 hours administer the aflibercept and continue 24 hour urine collection until the protein is 1g per 24 hours or less. For recurrent proteinuria reduce the dose to 2mg/kg. Treatment should be stopped where either nephrotic syndrome or thrombotic microangiopathy develop.

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.

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 0 or 1 of the National Cancer Institute Common Toxicity Criteria scale (NCI-CTC) within fourteen days. Diarrhoea must have resolved completely. Where a NCI-CTC grade 2 to 4 non-haematological event has occurred the irinotecan dose must be reduced to 150mg/m^2 in the first instance. If a second episode occurs despite this dose reduction delay until the symptoms have resolved and re-start the irinotecan at 100mg/m^2. Stop treatment for a third episode.

Regimen

14 day cycle for 6 cycles

Drug	Dose	Days	Route
Aflibercept	4mg/kg	1	Intravenous infusion in 100ml sodium chloride 0.9% over 60 minutes
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
Irinotecan	180mg/m^2	1	Intravenous infusion in 250ml sodium chloride 0.9% over 90 minutes

Dose Information

- Aflibercept will be dose banded according to the CSCCN agreed bands
- Fluorouracil will be dose banded in accordance with the national dose bands (25mg/ml PM bolus and 50mg/ml infusion)
- Irinotecan will be dose banded in accordance with the national dose bands (20mg/ml)

Administration Information

Extravasation

- Aflibercept - neutral
- Fluorouracil – inflammitant
- Irinotecan - irritant

Other

- Central venous access and use of an ambulatory infusion pump is required

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

- 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.

- 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 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

Additional Information

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

References
1. Van Cutsem E, Tabernero J, Lakomy R et al. Addition of aflibercept to fluorouracil. Leucovorin and irinotecan improves survival in a phase III randomised trial in patients with metastatic colorectal cancer previously treated with an oxaliplatin based regimen. J Clin Oncol 2012; 30: 3499-3506

REGIMEN SUMMARY

Aflibercept-Fluorouracil-Folinic Acid (MdG)-Irinotecan

Day One

1. Dexamethasone 8mg oral or intravenous

2. Ondansetron 8mg oral or intravenous

3. Aflibercept 4mg/kg in 100ml sodium chloride 0.9% over 60 minutes intravenous infusion

4. Atropine 250microgram subcutaneous for the prevention of irinotecan associated cholinergic symptoms

5. Irinotecan 180mg/m^2 in 250ml sodium chloride 0.9% over 90 minutes intravenous infusion

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

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

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

9. Atropine 250microgram subcutaneous when required for the treatment of irinotecan associated cholinergic symptoms

Take Home Medicines

9. Dexamethasone 4mg twice a day oral for 3 days starting on day two of the cycle

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

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1.1	Nov 2020	Updated monitoring with DPD testing Dose banding updated Coding removed	Donna Kimber Pharmacy Technician	Rebecca Wills Pharmacist
1	July 2014	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 Hospitals NHS Foundation Trust
University Hospital Southampton NHS Foundation Trust
Western Sussex Hospitals NHS Trust

All actions have been taken to ensure these protocols are correct. However, it remains the responsibility of the prescriber to ensure the correct drugs and doses are prescribed for patients.