Chemotherapy Protocol

COLORECTAL CANCER

CETUXIMAB(500)-FLUOROURACIL-FOLINIC ACID (Modified de Gramont)-IRINOTECAN

This regimen may require funding

Regimen

- Colorectal Cancer – Cetuximab(500)-Fluorouracil-Folinic Acid (modified de Gramont)-Irinotecan

Indication

- Cetuximab in combination with a fluoropyrimidine and irinotecan chemotherapy is recommended as a possible first or second line treatment for people with metastatic colorectal cancer when:

  - surgery to remove the cancer in the colon or rectum has been carried out or is possible
  - the metastases are only in the liver and cannot be removed surgically before treatment
  - the person is fit enough to have surgery to remove the cancer in the colon or rectum and to have liver surgery if it becomes possible to remove the metastases after cetuximab treatment
  - there is a contra-indication or the individual is intolerant to oxaliplatin

- The tumour is positive for the wild type KRAS genotype

- WHO performance status 0, 1

Toxicity

Drug	Adverse Effect
Cetuximab	Infusion related reactions, interstitial lung disease, skin reactions, electrolyte abnormalities, fatigue, abdominal pain, constipation
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

- Prior to starting therapy confirm a positive KRAS status

- FBC, LFT's and U&E's prior to day one of treatment

- Monitor for hypersensitivity reactions for 60 minutes after the end of the cetuximab infusion

- 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

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 restart 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.

There is little need to adjust the dose of cetuximab 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
Cetuximab	Administer only when the transaminases are 5xULN or below and the bilirubin is 1.5xULN or below	Administer only where the serum creatinine is 1.5xULN or below
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% and for severe impairment by 50%	A dose adjustment is only required in severe renal impairment
Irinotecan	For the 350mg/m^2 dose if the bilirubin is 26 to 51 umol/L inclusive prescribe 200mg/m^2. If the bilirubin is above 51umol/L consider stopping therapy.	No adjustments are necessary although there is limited information

Other

Cetuximab

Allergic or hypersensitivity reactions have occurred during the administration of cetuximab. For a NCI-CTC grade 1 reaction reduce the infusion rate by 50%. For a NCI-CTC grade 2 reaction, stop the infusion and administer supportive therapies as indicated. Once the reaction has resolved to NCI-CTC grade 1 or below resume the infusion at 50% of the previous rate. For a NCI-CTC grade 3 or 4 toxicity stop the infusion immediately and disconnect the tubing from the patient. Administer appropriate supportive therapies. Once recovered, patients should not receive cetuximab again.

Once the rate has been reduced it should not be increased on subsequent infusions.

If a second reaction occurs on the slower infusion rate the infusion should be stopped and no further treatment given.

An acniform skin rash occurs in over 70% of those receiving cetuximab. The onset is normally within three weeks of starting therapy and often resolves after week twelve. For a NCI-CTC grade 1-2 reaction use symptomatic treatments such as topical or oral antibiotics and continue with the cetuximab. For a NCI-CTC grade 3 toxicity delay treatment until the toxicity resolves to NCI-CTC grade 2 or below. If this occurs within fourteen days resume cetuximab at the same dose. If more than fourteen days is required stop treatment. If the NCI-CTC grade 3 toxicity occurs for a second and third time the cetuximab may again be delayed for up to and including fourteen days with concomitant dose reductions. Cetuximab dose reductions are permanent. The cetuximab must be discontinued if more than two consecutive infusions are withheld or a fourth episode of NCI-CTC grade 3 skin toxicity develops.

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
Cetuximab	500mg/m^2	1	Intravenous infusion (see administration)
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

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

- Cetuximab - neutral
- Fluorouracil – inflammitant
- Irinotecan - irritant

Other

- Central venous access and use of an ambulatory infusion pump is required
- Individuals should be monitored for hypersensitivity for sixty minutes after finishing the cetuximab infusion. Do not administer other chemotherapy during this period.
- The rate of administration of cetuximab must not exceed 5mg/min for the first infusion (minimum 120 minutes). If this infusion rate is well tolerated subsequent infusions may be given at a rate of 10mg/min (minimum 60 minutes)
- Irinotecan may be administered over 30-90 minutes

Additional Therapy

- 30 minutes prior to cetuximab infusion;

  - chlorphenamine 10mg intravenous
  - dexamethasone 8mg oral or intravenous
  - H_2 antagonist according to local formulary choice and availability
  - paracetamol 1000mg oral

- Antiemetics

  15-30 minutes prior to chemotherapy

  - 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.

- 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

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

References
1. Moosmann N, Heinemann V. Cetuximab plus XELIRI or XELOX for the first line therapy of metastatic colorectal cancer.Clin Colorectal Cancer 2008; 7 (2): 110-117.
2. van Custen E, Kohne CH, Lang I et al. Cetuximab plus irinotecan, fluorouracil and leucovorin as first line treatment for metastatic colorectal cancer: Updated analysis of overall survival according to tumour KRAS and BRAF mutation status. JCO 2011; 29: 1-10.

REGIMEN SUMMARY

Cetuximab(500)-Fluorouracil-Folinic Acid (MdG)-Irinotecan

Day One

1. Chlorphenamine 10mg intravenous

2. Dexamethasone 8mg oral or intravenous

3. Paracetamol 1000mg oral
Administration Instructions
Please check if the patient has taken paracetamol. The maximum dose is 4000mg in every 24 hours

4. H_2 antagonist according to local formulary choice and availability
Administration Instructions:
Administer according to local formulary choice and availability one of the following 30 minutes prior to chemotherapy;
- Ranitidine 50mg intravenous once only
- Famotidine 20mg oral once only
- Nizatidine 150mg oral once only
- Ranitidine 150mg oral once only

If there is no stock of these products due to national shortages treatment may proceed without the H_2 antagonist provided there is no instruction in the ARIA journal indication the patient **must have** H_2 antagonist treatment.

All infusion related reactions must be recorded in the ARIA journal and reported to the appropriate consultant. Many Trusts do not administer an H_2 antagonist from cycle three onwards. They have been left in the ARIA protocols so that decisions can be made on an individual Trust and patient basis.

5. Cetuximab 500mg/m^2 intravenous infusion

An interval of 60 minutes should be left between administration of cetuximab and the remaining chemotherapy

6. Atropine 250microgram subcutaneous

7. Ondansetron 8mg oral or intravenous

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

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

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

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

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

Take Home Medicines

13. Dexamethasone 4mg twice a day oral for 3 days starting the day after irinotecan

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

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1.3	Nov 2020	Update of premedication due to shortage of IV ranitidine. IV ranitidine changed to H_2 antagonist according to local formulary choice and availability Coding removed Dose banding updated Updated monitoring with DPD testing	Donna Kimber Pharmacy Technician	Rebecca Wills Pharmacist
1.2	May 2014	Header changed Bolus removed from supportive therapies Irinotecan administration changed to 90 minutes Cetuximab administration changed in line with SPC Coding updated Metoclopramide dose changed to 10mg Disclaimer added Atropine added prior to irinotecan	Dr Debbie Wright Pharmacist	Donna Kimber Pharmacy Technician
1.1	Dec 2011	Numbers amended on the regimen summary page to run concurrently. Administration instruction for cetuximab added to the regimen summary page 500 added to the name of the regimen Ondansetron order of administration changed to be given after the cetuximab Footnote on page 7 changed from irinotecan to cetuximab Cycle one removed from the regimen section Day one removed from antiemetics Cetuximab dose modifications altered for skin toxicity.	Dr Debbie Wright Pharmacist	Donna Kimber Pharmacy Technician
1	Sept 2011	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 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.