Chemotherapy Protocol

COLORECTAL CANCER

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

Regimen

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

Indication

- Colorectal cancer with metastases confined to the liver where resection may become possible following treatment
- Metastatic or advanced colorectal cancer where surgery to remove the cancer in the colon or rectum has been conducted or is possible
- Metastatic or advanced colorectal cancer where the individual is sufficiently fit to undergo surgery to remove the cancer in the colon or rectum and to have a liver resection if it becomes possible to remove the metastasis following cetuximab
- 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
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
- 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

Consider blood transfusion if patient symptomatic of anaemia or has a haemoglobin of less than 8g/dL

For haematological toxicity, if the neutrophil count is less than 1.5×10^9/L or the platelet count is less than 75×10^9/L, then 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 then 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 stop therapy.

There is no need to dose adjust the folinic acid for haematological counts.

The dose of cetuximab on day eight need not be adjusted for either neutrophil or platelet counts.

Liver Impairment

Drug	Bilirubin µmol/L		AST/ALT units	Dose (% of original dose)
Cetuximab				Unlikely to require dose adjustment
Fluorouracil	More than 85		More than 180	Contra-indicated
				In moderate hepatic impairment reduce the initial dose by 33%. In severe hepatic impairment reduce the initial dose by 50%. The dose may be increased as tolerated.
Oxaliplatin				Limited information available but there is probably little need to adjust the dose.

Renal Impairment

Drug	Creatinine Clearance (ml/min)	Dose (% of original dose)
Cetuximab		Clinical decision. Unlikely to require a dose adjustment
Fluorouracil		Consider dose adjustment in sever renal impairment
Oxaliplatin		Moderate renal impairment – treat at normal dose, and monitor renal function. Dose adjust according to toxicity. CrCl <20m/min –dose reduce

Other

Cetuximab

Allergic or hypersensitivity reactions have occurred during the administration of cetuximab. For a grade 1 reaction reduce the infusion rate by 50%. For a grade 2 reaction, stop the infusion and administer supportive therapies as indicated. Once the reaction has resolved to grade 1 or below resume the infusion at 50% of the previous rate. For a 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 grade 1-2 reaction use symptomatic treatments such as topical or oral antibiotics and continue with the cetuximab. For a grade 3 toxicity delay treatment until the toxicity resolves to 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 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 to 200mg/m^2 and 150mg/m^2. Cetuximab dose reductions are permanent. The cetuximab must be discontinued if more than two consecutive infusions are withheld or a fourth episode of 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 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 grade 4 toxicity at any time stop fluorouracil therapy.

Oxaliplatin

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

If 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 to exclude an interstitial cause.

Regimen

14 day cycle for 8 cycles

Response to treatment is often assessed after 6 cycles of therapy.

Cycle 1

Drug	Dose	Days	Administration
Cetuximab	400mg/m^2	1	Intravenous infusion (see administration)
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
Fluorouracil	400mg/m^2	1	Intravenous bolus over 10 minutes
Fluorouracil	2400mg/m^2	1	Intravenous infusion over 46 hours
Cetuximab	250mg/m^2	8	Intravenous infusion over 60 minutes

Cycle Two Onwards

Drug	Dose	Days	Administration
Cetuximab	250mg/m^2	1	Intravenous infusion (see administration)
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
Fluorouracil	400mg/m^2	1	Intravenous bolus over 10 minutes
Fluorouracil	2400mg/m^2	1	Intravenous infusion over 46 hours
Cetuximab	250mg/m^2	8	Intravenous infusion over 60 minutes

Dose Information

- Cetuximab will be dose banded in accordance with the national dose bands (5mg/ml)
- Fluorouracil will be dose banded in accordance with the national dose bands (50mg/ml)
- Oxaliplatin will be dose banded in accordance with the national dose bands (5mg/ml)

Administration Information

Extravasation

- Cetuximab - neutral
- Fluorouracil – inflammitant
- Oxaliplatin - exfoliant

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. If this infusion rate is well tolerated subsequent infusions may be given at a rate not exceeding 10mg/min.
- A glucose 5% flush should be administered before and after the oxaliplatin

Additional Therapy

- 30 minutes prior to cetuximab infusion;

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

- Antiemetics

  15-30 minutes prior to chemotherapy on **day one** only

  - ondansetron 8mg oral or intravenous

As take home medication

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

No antiemetics are required on day 8 although cetuximab pre-medication is.

- 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).

- 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. Adams RA, Meade AM, Madi A et al. Toxicity associated with combination oxaliplatin plus fluoropyrimidine with or without cetuximab in the MRC COIN trial experience. British Journal of Cancer 2009; 100 (2): 251-258.

REGIMEN SUMMARY

Cetuximab-Fluorouracil-Folinic Acid (MdG)-Oxaliplatin

Cycle 1

Day 1

1. Chlorpheniramine 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 400mg/m^2 intravenous infusion

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

6. Ondansetron 8mg oral or intravenous

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

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

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

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

Day 8

11. Chlorpheniramine 10mg intravenous bolus

12. Dexamethasone 8mg oral or intravenous

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

14. 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

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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.

15. Cetuximab 250mg/m^2 intravenous infusion

Take Home Medicines (day one only)

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

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

Cycle 2

Day 1

1. Chlorpheniramine 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 250mg/m^2 over 60 minutes intravenous infusion

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

6. Ondansetron 8mg oral or intravenous

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

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

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

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

Day 8

11. Chlorpheniramine 10mg intravenous

12. Dexamethasone 8mg oral or intravenous

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

14. 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.

15. Cetuximab 250mg/m^2 over 60 minutes intravenous infusion

Take Home Medicines (day one only)

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

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

DOCUMENT CONTROL

Version	Date	Amendment	Written/Amended By	Approved By
1.5	October 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	Arum Shortland Pharmacist	Dr Debbie Wright Pharmacist
1.4	May 2014	Header changed Bolus removed from supportive therapies Intravenous added as a route to supportive therapies Stat removed from loperamide TTOs clarified Metoclopramide dose changed to 10mg Disclaimer added	Dr Debbie Wright Pharmacist	Donna Kimber Pharmacy Technician
1.3	January 2013	OPCS procurement code changed from X70.8 to X71.5. OPCS delivery code changed from X72.9 to X72.1. “An interval of 60 minutes should be left between the administration of cetuximab and oxaliplatin” added to regimen summary. Duration of administration of fluorouracil bolus changed to 10 minutes in regimen and regimen summary. Order of administration changed in regimen summary - ondansetron now after cetuximab and folinic acid after oxaliplatin. Tables inserted for renal and hepatic dose adjustments and regimen	Rebecca Wills Pharmacist	Dr Debbie Wright Pharmacist
1.2	Apr 2011	Document control changed to table Stat removed from additional therapy and regimen summary Pyridoxine removed from additional therapy	Dr Debbie Wright (Pharmacist)	Donna Kimber (Pharmacy Technician)

		Cetuximab changed to remove administration in glucose 5% > < symbols removed and replaced with the corresponding words Regimen name changed to have line between drug names and also added to the regimen summary Folinic Acid added to footer Cetuximab monitoring moved from “additional points” to “administration information” Cetuximab administration changed to 60 minutes on day 8 of cycle 1		
1.1	Jan 2011	Oxaliplatin changed to be administered in 500ml glucose 5% Spelling of forth changed to fourth on page 3 Remove duplication of word ‘reaction’ on page 3 Add bolus to statement at bottom of page 8	Dr Debbie Wright (Pharmacist)	Donna Kimber (Pharmacy Technician)
1	Aug 2010	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.