Chemotherapy Protocol

COLORECTAL CANCER

FLUOROURACIL, FOLINIC ACID (Modified de Gramont), OXALIPLATIN and PANITUMUMAB

(FOLFOX-Panitumumab)

Regimen

- Colorectal Cancer– Fluorouracil, Folinic Acid (modified de Gramont), Oxaliplatin and Panitumumab (FOLFOX-Panitumumab)

Indication

- First metastatic colorectal cancer where the following criteria are met;

  - the tumour is wild type RAS
  - no prior exposure to either cetuximab or panitumumab

- WHO Performance status 0, 1

Toxicity

Drug	Adverse Effect
Fluorouracil	Palmar-plantar erythrodysesthesia, diarrhoea, mucositis, chest pain
Oxaliplatin	Peripheral neuropathy (cumulative), acute laryngopharyngeal dysasthesia (increase duration of infusion)
Panitumumab	Infusion related reactions, interstitial lung disease, skin reactions, electrolyte abnormalities, fatigue, abdominal pain, constipation

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

Monitoring

Regimen

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

- Prior to starting therapy confirm a positive wild type RAS status

- 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 or erythropoietin if the patient is 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, 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 then 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 more stop therapy. The panitumumab dose rarely needs to be reduced for haematological toxixity but may be delayed.

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

Liver Impairment

Drug	Bilirubin µmol/L		AST/ALT units	Dose (% of original dose)
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.
Panitumumab	No information available			

Renal Impairment

Drug	Creatinine Clearance (ml/min)	Dose (% of original dose)
Fluorouracil		Consider dose adjustment in sever renal impairment
Oxaliplatin		For moderate renal impairment, treat at normal dose, and monitor renal function. Dose adjust according to toxicity. If the CrCl is less than 20m/min then dose reduce
Panitumumab	No information available	

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. Dose limiting toxicities include diarrhoea, abdominal pain, emesis, stomatitis, palmar-plantar erythrodysesthesia and neurosensory toxicities among others.

If any NCI-CTC grade 1 toxicity occurs treatment should be continued, without interruption, at the full dose.

For toxicities at NCI-CTC grade 3 or above treatment should be withheld until recovery to NCI-CTC grade 1 then re-started if medically appropriate. If recovery takes 21 days or longer stop treatment.

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. 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. After resolution of a third episode of NCI-CTC grade 2 diarrhoea to NCI-CTC grade 1 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 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 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 ant time stop fluorouracil therapy.

Oxaliplatin

If the neurosensory toxicity is NCI-CTC grade 1–2 and lasts less than 7 days administer full dose oxaliplatin. If the toxicity is NCI-CTC grade 2 and persists for more than 7 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 to exclude an interstitial cause.

Panitumumab

An acniform skin rash occurs in over 90% of those receiving panitumumab. The onset is normally within three weeks of starting therapy and often resolves after week twelve. Please refer to local guidelines for the treatment of this reaction. Alternatively, for a NCI-CTC grade 1-2 reaction use symptomatic treatments such as topical or oral antibiotics and continue with the panitumumab. For a NCI-CTC grade 3 toxicity delay treatment until the toxicity resolves to NCI-CTC grade 2 or below. Re-instate therapy using 50% of the original dose. If the reaction does not recur escalate the dose in 25% increments as tolerated until the recommended dose is reached. If the reactions do not resolve to less than NCI-CTC grade 2 after withholding up to two doses or if the skin toxicity recurs or becomes intolerable at 50% of the original dose discontinue treatment.

UV radiation may worsen skin reactions. Sun safety practices should be followed during and for up to two months after the end of treatment.

Stop treatment if there is a confirmed pneumonitis.

Regimen

14 day cycle for 6 cycles

Drug	Dose	Days	Administration
Folinic Acid	350mg	1	Intravenous infusion in 250ml glucose 5% over 120 minutes
Oxaliplatin	85mg/m^2 (maximum dose 170mg)	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
Panitumumab	6mg/kg	1	Intravenous infusion in 100ml sodium chloride 0.9% over 60 minutes (see administration instructions)

Dose Information

- 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)
- Oxaliplatin dose will be capped at 170mg.
- Panitumumab will be dose banded in accordance with the national dose bands (20mg/ml NS)

Administration Information

Extravasation

- Fluorouracil – inflammitant
- Oxaliplatin – exfoliant
- Panitumumab - neutral

Other

- Central venous access and use of an ambulatory infusion pump may be required.
- Panitumumab must be administered using a 0.22 micron in-line filter
- Doses of 1000mg and above must be administered over 90 minutes in 150ml sodium chloride 0.9%

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

- 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).
- Prophylaxis for skin rash according to local formulary choices. For example;

- doxycycline 100mg twice a day for 14 days oral
- lymecycline 408mg once a day for 14 days oral

- Gastric protection with a proton pump inhibitor or H_2 antagonist may be considered in patients considered at high risk of GI ulceration or bleed

Additional Information

- A glucose 5% flush should be administered before and after the oxaliplatin

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

References
1. Douillard JY, Oliner KS, Siena S et al. Panitumumab-FOLFOX4 treatment and RAS mutations in colorectal cancer. N Engl J Med 2013; 369 (11): 1023-1034.

REGIMEN SUMMARY

Flourouracil-Folinic Acid (MdG)-Oxaliplatin-Panitumumab (FOLFOX-Panitumumab)

Day One

1. Panitumumab 6mg/kg intravenous infusion in 100ml sodium chloride 0.9% over 60 minutes*

2. Dexamethasone 8mg oral or intravenous

3. Ondansetron 8mg oral or intravenous

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

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

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

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

Take Home Medicines

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

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

9. Skin Rash Prophylaxis
   Administration Instructions

   For the prevention of skin reactions according to local formulary choice;
   - doxycycline 100mg twice a day for 14 days oral
   - lymecycline 408mg once a day for 14 days oral

*Please refer to the administration instructions

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	May 2016	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 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.