Chemotherapy Protocol

COLORECTAL CANCER

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

(FOLFIRI-Panitumumab)

This protocol may require funding

Regimen

- Colorectal Cancer– Fluorouracil, Folinic Acid (Modified de Gramont), Irinotecan and Panitumumab (FOLFIRI-Panitumumab)

Indication

- The first line treatment of metastatic colorectal cancer where the following criteria are met;

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

- WHO performance status 0, 1, 2

- Palliative intent

Toxicity

Drug	Adverse Effect
Fluorouracil	Palmar-plantar erythrodysesthesia, diarrhoea, mucositis, chest pain
Irinotecan	Acute cholinergic syndrome, diarrhoea (may be delayed)
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, U&E's and LFT's on day one of the cycle

- 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

Prior to prescribing 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 or erythropoietin if the patient is 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 7 days. Only re-start treatment when these levels are reached and omit the bolus fluorouracil. If a 14 day delay is required to allow counts to recover or there are two separate delays of 7 days during treatment then the bolus dose of fluorouracil should be omitted and the irinotecan reduced by 20%. Consider also reducing the dose of the infusional fluorouracil dose by 20%.

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 dose should be reduced by 20% of the original dose.

There is no need to dose adjust the folinic acid for haematological toxicity. The panitumumab dose is not often reduced for haematological toxicity but may be delayed.

Kidney / Liver Impairment

Drug	Hepatic	Renal
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	No data is available for dose modification of irinotecan in combination with fluorouracil. However, consideration should be given to dose reduction if bilirubin is greater than 1.5xULN and less than 3xULN. Irinotecan is contra-indicated if bilirubin is more than 3xULN.	No adjustments are necessary although there is limited information
Panitumumab	No information available	No information available

Other Toxicities

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). 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.

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 treatment guidelines. 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	Route
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
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)
- Irinotecan will be dose banded in accordance with the national dose bands (20mg/ml)
- The maximum daily dose of irinotecan is 360mg
- Panitumumab will be dose banded in accordance with the national dose bands (20mg/ml NS)

Administration Information

Extravasation

- Fluorouracil – inflammitant
- Irinotecan – irritant
- Panitumumab - neutral

Other

- Central venous access and use of an ambulatory infusion pump is required
- Irinotecan may be administered over 30-90 minutes
- Panitumumab must be administered using a 0.22 micron in-line filter
- Panitumumab 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 on **day one** only;

  - 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

- 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.

- 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

- Consider oral ciprofloxacin 500mg twice a day where diarrhoea continues for more than 24 hours. Review the patient before starting this treatment.

- Mouthwashes as per local or national guidelines for the treatment of mucositis

- 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. Peeters M, Price TJ, Cervantes A et al. Randomised phase III study of panitumumab with fluorouracil, leucovorin and irinotecan (FOLFIRI) compared with second line treatment in patients with metastatic colorectal cancer.

REGIMEN SUMMARY

Fluorouracil-Folinic Acid (MdG)-Irinotecan-Panitumumab (FOLFIRI-Panitumumab)

Day One

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

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

3. Dexamethasone 8mg oral or intravenous

4. Ondansetron 8mg oral or intravenous

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

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

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

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

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

Take Home Medicines

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

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

12. 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.