Chemotherapy Protocol

COLORECTAL CANCER

FLUOROURACIL, FOLINIC ACID (Modified de Gramont) and IRINOTECAN

(FOLFIRI)

Regimen

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

Indication

- Treatment of advanced/metastatic colorectal cancer
- 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)

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 prior to each cycle
- 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 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 7 days. Only re-start treatment when these levels are reached. Resume the fluorouracil at the original dose. The irinotecan dose should be reduced to 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 then the bolus dose of fluorouracil should be omitted and / or the irinotecan reduced 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 to 80% of the original dose.

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

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	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 Toxicities

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.

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

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 700mg.

Administration Information

Extravasation

- Fluorouracil – inflammitant
- Irinotecan - irritant

Other

- Central venous access and use of an ambulatory infusion pump may be required
- Irinotecan may be administered over 30-90 minutes

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.

- 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. Leonard P, Seymour MT, James R et al. Phase II study of irinotecan with bolus and high dose infusional 5-FU and folinic acid (modified de Gramont) for first or second line treatment of advanced or metastatic colorectal cancer. Br J Cancer 2002; 87 (11): 1216-1220.

REGIMEN SUMMARY

Day One

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

2. Dexamethasone 8mg oral or intravenous

3. Ondansetron 8mg oral or intravenous

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

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

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

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

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

Take Home Medicines

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

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

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1.2	Nov 2020	Updated monitoring with DPD testing Dose banding updated Coding removed	Donna Kimber Pharmacy Technician	Rebecca Wills Pharmacist
1.1	May 2014	Header changed Toxicities removed Tabulation throughout Hepatic and renal dose reductions updated Irinotecan changed to 90 minutes Twice daily changed to twice a day Bolus removed from supportive treatments Atropine added as a standard treatment before irinotecan Metoclopramide dose changed to 10mg Pyridoxine removed from supportive therapies Mouthwash recommendations updated Coding updated Disclaimer added	Dr Debbie Wright Pharmacist	Donna Kimber Pharmacy Technician
1	Aug 2010		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 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.