

Chemotherapy Protocol

COLORECTAL CANCER

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

Regimen

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

Indication

- First / second line treatment of advanced / metastatic colorectal cancer.
- Adjuvant treatment of stage III colon cancer following surgery.
- WHO Performance status 0, 1

Toxicity

Drug	Adverse Effect
Fluorouracil	Palmar-plantar erythrodysesthesia, diarrhoea, mucositis, chest pain
Oxaliplatin	Peripheral neuropathy (cumulative), acute laryngopharyngeal dysaesthesia (increase duration of infusion)

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
- 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 $1.5 \times 10^9/L$ or the platelet count less than $75 \times 10^9/L$, delay treatment until these levels are achieved. Reinitiate therapy at the full dose for up to a 7 day delay or, for a delay of more than 7 days, with 75% of the original dose for thrombocytopenia. If neutropenia is the issue after 7 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 ≥ 21 days stop therapy.

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

Liver Impairment

Drug	Bilirubin $\mu\text{mol/L}$		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.

Renal Impairment

Drug	Creatinine Clearance (ml/min)	Dose (% of original dose)
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

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 any 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/m². 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/m².

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 6 - 12 cycles

Drug	Dose	Days	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

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)

Administration Information

Extravasation

- Fluorouracil – inflammitant
- Oxaliplatin - exfoliant

Other

- Central venous access and use of an ambulatory infusion pump is required.

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).
- Gastric protection with a proton pump inhibitor or H₂ 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. Cheeseman SL, Joel SP, Chester JD et al. A "modified de Gramont" regimen of fluorouracil, alone and with oxaliplatin, for advanced colorectal cancer. Br J Cancer 2002; 87 (4): 393-9.

REGIMEN SUMMARY

Day One

1. Dexamethasone 8mg oral or intravenous
2. Ondansetron 8mg oral or intravenous
3. Oxaliplatin 85mg/m² intravenous infusion in 500ml glucose 5% over 120 minutes
4. Folinic Acid 350mg in 250ml glucose 5% over 120 minutes intravenous infusion
5. Fluorouracil 400mg/m² intravenous bolus over 10 minutes
6. Fluorouracil 2400mg/m² 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

DOCUMENT CONTROL

Version	Date	Amendment	Written/ By	Approved By
1.4	Nov 2020	Updated monitoring with DPD testing Dose banding updated Coding removed	Donna Kimber Pharmacy Technician	Rebecca Wills Pharmacist
1.3	May 2014	Header changed Intravenous added to supportive therapies PO changed to oral Metoclopramide dose changed to 10mg Dexamethasone TTO clarified Coding updated Disclaimer added	Dr Debbie Wright Pharmacist	Donna Kimber Pharmacy Technician
1.2	January 2013	Document control table added. OPCS procurement code changed from X70.5 to X70.4. Duration of administration of fluorouracil bolus changed to 10 minutes in regimen and regimen summary. Order of administration changed in regimen summary – folinic acid now after oxaliplatin. Information on dose, liver and renal impairment put into tables.	Rebecca Wills Pharmacist	Dr Debbie Wright Pharmacist
1.1	January 2011	Oxaliplatin changed to be administered in 500ml glucose 5%.	Dr Debbie Wright Pharmacist	Donna Kimber Pharmacy Technician
1	August 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 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.

