FOLFOX - Oxaliplatin and Modified de Gramont Fluorouracil (colorectal)

Indication

Adjuvant treatment of stage III colon cancer after complete resection of the primary tumour.

First or second line chemotherapy for metastatic colorectal cancer.

(NICE CG131)

ICD-10 codes

Codes prefixed with C18-20.

Regimen details

Day	Drug	Dose	Route
1	Calcium folinate	350mg	IV infusion
1	Oxaliplatin	85mg/m^2	IV infusion
1	Fluorouracil	400mg/m^2	IV bolus
1-2 (46 hours)	Fluorouracil	2400mg/m^2	IV infusion over 46 hours

Cycle frequency

14 days

Number of cycles

6 cycles then review. Maximum 12 cycles.

Administration

Oxaliplatin is administered in 250mL glucose 5% over 2 hours. This is infused **concurrently** with calcium folinate in 250mL glucose 5% over 2 hours.
The line should then be flushed with glucose 5%.

Patients should be observed closely for platinum hypersensitivity reactions, particularly during the first and second infusions. Hypersensitivity reactions may occur within a few minutes following the initiation of the infusion of oxaliplatin. Facilities for the treatment of hypotension and bronchospasm must be available.
If hypersensitivity reactions occur, minor symptoms such as flushing or localised cutaneous reactions do not require discontinuation of therapy: the infusion may be temporarily interrupted and when symptoms improve re-started at a slower infusion rate. Chlorphenamine 10mg IV may be administered.
Severe reactions, such as hypotension, bronchospasm or generalised rash/erythema require immediate discontinuation of oxaliplatin and appropriate therapy should be initiated.

Oxaliplatin may cause transient paraesthesia of hands and feet and laryngopharyngeal dysaesthesia (unpleasant sensations in the throat). Onset is during or within hours of infusion and resolves within minutes to a few days. Symptoms are exacerbated by cold, so patients should be well advised on precautions to be taken. This does not require treatment or dose reduction but subsequent infusions should be given over 6 hours.

Fluorouracil is administered as an IV bolus injection over 5 minutes.
Fluorouracil infusion is administered either via a central venous catheter and ambulatory infusion device over 46 hours or as a continuous peripheral IV infusion over 46 hours in 2 x 1000mL sodium chloride 0.9%.

Pre-medication

Antiemetics as per local policy.
Patients who have previously experienced Grade 1 or 2 platinum hypersensitivity should receive the following premedication:

- 45 minutes prior to Oxaliplatin: Dexamethasone 20mg IV
- 30 minutes prior to Oxaliplatin: Chlorphenamine 10mg IV and Ranitidine 50 mg IV

Patients who develop peripheral neuropathy may be considered for calcium gluconate 1g and magnesium sulphate 1g given together in 250mL 5% glucose IV over 20 minutes pre- and post-oxaliplatin infusion. Caution is required in giving this treatment to patients with known hypercalcemia or those receiving therapy with digoxin or thiazide diuretics.

Emetogenicity

This regimen has a moderate-high emetogenic potential

Additional supportive medication

Mouthwashes as per local policy.
Loperamide if required.

Extravasation

Oxaliplatin is an exfoliant (Group 4).
Fluorouracil is an inflammatant (Group 2).

Investigations – pre first cycle

Investigation	Validity period
FBC	14 days
U+E (including creatinine)	14 days
LFTs	14 days
Calcium	14 days
CEA	14 days

Investigations - pre subsequent cycles

Investigation	Validity period
FBC	96 hours
U+E (including creatinine)	7 days
LFTs	7 days
Calcium	7 days
CEA	Monthly

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant.

Investigation	Limit
Neutrophils	≥ 1.0 x 10^9/L
Platelets	≥ 75 x 10^9/L
Bilirubin	< 1.5 x ULN
AST/ALT	< 3 x ULN
Creatinine Clearance (CrCl)	≥ 50mL/min

Dose modifications

- **Haematological toxicity**

Defer treatment for 1 week if neutrophil count <1.0 x 10^9/L and/or platelets < 75 x 10^9/L.

If platelets 10-49 x 10^9/L defer until ≥ 75 x 10^9/L and reduce oxaliplatin dose to 65mg/m^2 (if second occurrence reduce oxaliplatin dose to 55mg/m^2).

If platelets < 10 x 10^9/L defer until ≥ 75 x 10^9/L and reduce oxaliplatin dose to 55mg/m^2 (if second occurrence – discuss with consultant).

If febrile neutropenia (neutrophils < 0.5 x 10^9/L and fever requiring IV antibiotics) – reduce all subsequent doses of fluorouracil to 50% and oxaliplatin dose to 55mg/m^2.

- **Renal impairment**

CrCl (mL/min)	**Oxaliplatin dose**	**Fluorouracil dose**
≥ 50	100%	100%
30-49	50%	100%
10-29	Omit	100%
< 10	Omit	Consider dose reduction

- **Hepatic impairment**

Bilirubin (x ULN)		**AST/ALT (x ULN)**	**Oxaliplatin dose**	**Fluorouracil dose**
≤ 1.5	and	≤ 1.5	100%	100%
1.5 - 3	and	≤ 3	100%	Consider dose reduction*
3 – 5	or	3 – 5	50%	Consider dose reduction*
> 5	or	> 5	omit	Contraindicated

*consultant decision

Note that significantly impaired hepatic function may be a sign of disease progression and require cessation of, or change in, treatment.

- **Other toxicities**

For all toxicities, delay treatment until resolved to ≤ Grade 1. Then reduce doses as per the following table:

Toxicity	**Definition**	**Oxaliplatin dose**	**Fluorouracil dose**
Diarrhoea*	Grade 2	100%	80%
	Grade 3	65mg/m^2	50%
	Grade 4	Discontinue treatment	
Stomatitis/Mucositis	Grade 2	100%	80%
	Grade 3	65mg/m^2	50%
	Grade 4	Discontinue treatment	
Palmar-Plantar erythema	Grade 2	100%	80%
	Grade 3/4	100%	50%
Peripheral neuropathy	Grade 2/3	65mg/m^2	100%
	Grade 4	Discontinue	100%

* Patients presenting with diarrhoea must be carefully monitored until the symptoms have disappeared completely, since a rapid (sometimes fatal) deterioration can occur. For diarrhoea ≥ grade 3, add ciprofloxacin 250mg BD.

Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects**

Myelosuppression
Infertility
Allergic reactions
Neurotoxicity
Coronary artery spasm*

*Coronary artery spasm is a recognised complication of fluorouracil treatment, although the evidence base regarding aetiology, management and prognosis is not particularly strong.
Coronary artery spasm is more common in patients receiving continuous infusions of fluorouracil, and is usually reversible on discontinuing the infusion. Should a patient receiving fluorouracil present with chest pains, stop the treatment. Standard investigation and treatment of angina may be required. If re-challenge is deemed necessary, this can be performed under close supervision, but should symptoms redevelop, the fluorouracil should be permanently discontinued.

- **Frequently occurring side effects**

Nausea and vomiting
Diarrhoea
Stomatitis and mucositis
Palmar-plantar erythema
Alopecia
Fatigue
Dyspnoea

- **Other side effects**

Transient cerebellar syndrome
Confusion

Significant drug interactions – for full details consult product literature/ reference texts

Oxaliplatin:
Avoid nephrotoxic agents as these may increase toxicity of oxaliplatin.

Fluorouracil:
Folinates: Avoid concomitant use of folinic and folic acid – enhanced toxicity of fluorouracil.
Co-trimoxazole/trimethoprim: Avoid if possible – enhances antifolate effect. If essential, monitor FBC regularly.
Warfarin/coumarin anticoagulants: Avoid use due to elevations in INR. Switch to low molecular weight heparin during treatment.

Additional comments

Dihydropyrimidine dehydrogenase (DPD) deficiency can result in severe toxicity secondary to reduced fluorouracil metabolism (this can present as severe diarrhoea and/or severe stomatitis early in the first cycle). Avoid use in patients with known DPD deficiency.

Cardiotoxicity has been associated with fluoropyrimidine therapy, with adverse events being more common in patients with a prior history of coronary artery disease. Caution must be taken in patients with a history of significant cardiac disease, arrhythmias or angina pectoris.

Dose related peripheral sensory neuropathy can occur with oxaliplatin. It usually occurs after a cumulative dose of 800mg/m2. It can occur after treatment with oxaliplatin is completed, and is usually reversible, taking approximately 3 – 5 months to recovery.

References

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