FOLFOX - Oxaliplatin and Modified de Gramont Fluorouracil (colorectal)

Indication

Neo-adjuvant chemotherapy as part of TNT (total neoadjuvant therapy) for rectal cancer.

> Patients initially receive pelvic radiotherapy either long (25 fractions), or short (5 fractions) course. TNT chemotherapy regime should aim to commence 2-3 weeks following completion of radiotherapy.

Neoadjuvant chemotherapy for colorectal cancer

Adjuvant chemotherapy for colorectal cancer

Metastatic colorectal cancer

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

Neo-adjuvant TNT: 9 cycles
Neo-adjuvant: 6 cycles
Adjuvant: 12 cycles
Metastatic: continue until disease progression

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:

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

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 (including AST)	14 days
Calcium	14 days
CEA	14 days
DPYD mutation testing	none
Hepatitis B serology (HBsAG, HBcAb)	none
HbA1c	3 months
Random glucose	14 days
ECG	28 days
Calculated Creatinine Clearance	14 days

Investigations - pre subsequent cycles

FBC, U&Es, LFT (including AST), calculated creatinine clearance, calcium, magnesium, random

glucose, CEA

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	≥ 1.5 x 10^9/L (discuss with consultant ≥ 1.0- <1.5)
Platelets	≥ 75 x 10^9/L
Bilirubin	< 1.5 x ULN
AST/ALT	< 1.5 x ULN
Creatinine Clearance (CrCl)	≥ 50mL/min (see dose modifications below)

For treatment with neoadjuvant and adjuvant intent consultants may be happy to proceed with Neutrophils ≥1.0 x 10^9/L and should document this.

Dose modifications

- **DPYD variants**

All patients due to receive fluoro-pyrimidine based therapy should have a DPD test prior to starting treatment. 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).

Any patient who has not had a DPD test should be discussed with the consultant prior to going ahead. Patients with variants should be considered for a dose modification following national advice for recommended dose adjustments.

https://www.uksactboard.org/_files/ugd/638ee8_4d24d37a598c485d9ef4d1ba90abccd5.pdf

Where a patient has had significant toxicities but the DPD test has shown none of the variants to be present, a further test can be conducted to test the presence of rarer variants.

- **Haematological toxicity**

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

Neutrophils	Platelets	Oxaliplatin dose	5 Fluoruracil dose
≥1.0 and	≥75	100%	100%
0.5-0.9 or	50-74	65mg/m^2	100%
<0.5 and/or	25-49	65mg/m^2	100%
<0.5 and/or	<25	55mg/m^2	100%

If febrile neutropenia (neutrophils < 0.5 x 10^9/L and fever requiring IV antibiotics) – reduce 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	100%	100%

10-29	65mg/m^2	100%
< 10	Omit	Consider dose reduction

- **Hepatic impairment**

Bilirubin (x ULN)		AST/ALT (x	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

- **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%

* Patients presenting with diarrhoea must be carefully monitored until the symptoms have disappeared completely, since a rapid (sometimes fatal) deterioration can occur.

Neurological toxicity:

Dose related peripheral neuropathy can occur with oxaliplatin. It usually occurs after a cumulative dose of 800mg/m^2. It can occur once oxaliplatin is completed.

If neurological symptoms occur, use the following oxaliplatin dose adjustments:

Toxicity grade	Oxaliplatin
1 (any duration) or grade 2 longer than 7 days	100%
2 paraesthesia persisting until next cycle	75mg/m^2
3 paraesthesia lasting longer than 7 days	75mg/m^2
3 paraesthesia persisting until next cycle	Discontinue permanently
4 of any duration	Discontinue permanently

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

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.

Fertility/Contraception

Patients should agree to use an acceptable method of birth control to avoid pregnancy for the duration of treatment and for 6 months afterwards. Breast feeding should be discontinued during treatment. Oxaliplatin may have an anti-fertility effect.

References

- Colorectal NICE guideline NG151 (updated 15 Dec 2021) accessed 17 April 2025
- Summary of Product Characteristics (Oxaliplatin) accessed 17 April 2025 via www.medicines.org.uk
- Summary of Product Characteristics (Fluorouracil) accessed 17 April 2025 via www.medicines.org.uk
- Personalised Medicine Approach for Fluoro-pyrimidine-based Therapies. UK Chemotherapy Board V2 September 2024 accessed 17 April 2025 via https://www.uksactboard.org/_files/ugd/638ee8_4d24d37a598c485d9ef4d1ba90abccd5.pdf
- Bahadoer R, Dijkstra E et al. Short Course radiotherapy followed by chemotherapy before total mesorectal excision (TME) versus pre-operative chemoradiotherapy, TME, and optional adjuvant chemotherapy in locally advanced rectal cancer (RAPIDO): a randomized, open-label, phase 3 trial The Lancet 2021 22(1): 29-42

THIS PROTOCOL HAS BEEN DIRECTED BY DR WILLIAMSON DESIGNATED LEAD CLINICIAN FOR COLORECTAL CANCER
RESPONSIBILITY FOR THIS PROTOCOL LIES WITH THE HEAD OF SERVICE

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