FOLFOXIRI

Indication

Metastatic colorectal cancer

Regimen details

Day	Drug	Dose	Route
1	Irinotecan	165mg/m^2	IV infusion
1	Oxaliplatin	85mg/m^2	IV infusion
1	Folinic Acid	350mg	IV infusion
1-2 (46 hours)	5 Fluorouracil	3200mg/m^2	46 hours in infusor pump

Nb Atropine 250mcg *must* be prescribed before treatment commences. This is only to be administered in the event of a cholinergic reaction unless the patient has experienced such a reaction in a previous cycle.

Cycle frequency

14 days

Number of cycles

Neo-adjuvant: 6 cycles
Metastatic: Until disease progression or unacceptable toxicity

Administration

Patient needs central line insertion.
Administer atropine 0.25mg s/c if patient experiences cholinergic reaction with first cycle
Warning: administering irinotecan and folinic acid concurrently in the same line may result in precipitation

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.

Oxaliplatin is given over 2 hours
Irinotecan is given over 30-90 minutes

Emetogenicity

This regime has a moderate emetogenic potential

Additional supportive medication

All patients must have access to loperamide with the advice to take 4mg at the onset of diarrhoea and to continue taking 2mg every 2 hours for at least 12 hours to a maximum of 48 hours (up to a maximum of 24mg/24 hours).

Pegfilgrastim 6mg given 24 hours after pump removal

Extravasation

Oxaliplatin is an exfoliant (Group 4)
Irinotecan is an irritant (Group 3).
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)

If only Hb is low (below 95g/dl) please contact doctor to arrange for blood transfusion but continue with chemotherapy

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.

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.

UGT1A1 poor metabolisers

Patients that are UGT1A1 poor metabolisers, such as patients with Gilbert's syndrome (eg homozygous for UGT1A1*28 or *6 variants) are at increased risk for severe neutropenia and diarrhoea following irinotecan treatment. This risk increases with irinotecan dose level. A reduced starting dose should be considered.

Renal impairment

Creatinine Clearance (ml/min)	Irinotecan dose	Oxaliplatin dose	5FU dose
>50	100%	100%	100%
30-50	Unclear guidance discuss	100%	100%
<30	Omit	Omit	80%

Hepatic impairment

Irinotecan and metabolites are cleared by biliary excretion. Data is not available in patients with hepatic impairment treated with irinotecan in combination.
Note that significantly impaired hepatic function may be a sign of disease progression and require cessation of, or change in, treatment.
Weekly monitoring of complete blood counts should be considered in patients with bilirubin from 1.5 to 3 times ULN due to decrease in the clearance of irinotecan and increased risk of hepatotoxicity in this population.

Bilirubin	ALP	Irinotecan dose	Oxaliplatin	5FU dose
<1.5 x ULN **and**	≤ 5 x ULN	100%	100%	100%
1.5-3 x ULN **or**	>5 x ULN	50%	100%	100%
>3 x ULN	any	Omit	50%	50%

Haematological toxicity

Grade I/II ANC	No dose reduction
Grade III/IV	Delay until recovered then proceed with 20% Irinotecan, oxaliplatin and 5FU reduction
If delay >1 week	reduce oxaliplatin, 5FU and irinotecan dose by 20%.

Continue at reduced dose for subsequent cycles unless other toxicity occurs
If further delays for bone marrow suppression occur despite a 20% dose reduction consider further 20% dose reduction

Immediate (within 24 hours)	Incidence low due to use of atropine pre-med	Further dose of atropine 250 mcg stat
Delayed (>24 hours after irinotecan up to any time before next cycle)	Initial treatment	Treat early with high dose loperamide (up to a max of 24mg/24 hr)
	Lasts >24 hours	Add ciprofloxacin 500mg bd
	Lasts >48 hours	If >48 hours or symptoms of dehydration admit for rehydration and supportive management
	Grade 3-4	Manage as above, then delay further treatment until recovery then resume at Irinotecan 80% dose 5FU 80% dose
	Unresolved before next cycle	Delay 1 week

Patients presenting with diarrhoea must be carefully monitored until the symptoms have disappeared as a rapid deterioration can occur

Other dose modifications should be made as per the following table

Toxicity grade	**1st occurrence**	**2nd occurrence**	**3rd occurrence**	**4th occurrence**
0-1	100%	100%	100%	100%
2	Delay then 100%	Delay then 75%	Delay then 50%	Discontinue
3	Delay then 75%	Delay then 50%	Discontinue	
4	Delay then 50%	Discontinue		

Any delays should be until toxicity has resolved to grade 0-1

Hand foot syndrome ≥ grade 2: 20% dose reduction of 5FU

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

Serious side effects

Myelosuppression
Infertility
Anaphylaxis
Neurotoxicity
Interstitial lung disease
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.

Irinotecan: Irinotecan is a major substrate of **cytochrome P450 CYP2B6 and CYP3A4** and as such levels of irinotecan may be reduced by medicines that induce levels of these enzymes. Conversely, levels of irinotecan may be increased by medicines that inhibit these enzymes.
Prochlorperazine should be avoided on the same day as irinotecan treatment due to the increased incidence of akathisia.

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. There is no data on fertility effect of irinotecan.

References

- Colorectal NICE guideline NG151 (updated 15 Dec 2021) accessed 9 May 2025 via www.nice.org.uk
- Summary of Product Characteristics (Oxaliplatin) accessed 26 June 2025 via www.medicines.org.uk
- Summary of Product Characteristics Irinotecan accessed 26 June 2025 via www.medicines.org.uk
- Summary of Product Characteristics Fluorouracil accessed 26 June 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

THIS PROTOCOL HAS BEEN DIRECTED BY DR WILLIAMSON, CONSULTANT ONCOLOGIST

RESPONSIBILITY FOR THIS PROTOCOL LIES WITH THE HEAD OF SERVICE

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