# FOLFOXIRI – Oxaliplatin, Irinotecan and Fluorouracil

## Indication

First or subsequent line treatment of advanced, unresectable metastatic colorectal cancer. Subsequent line use following previous fluorouracil based adjuvant chemotherapy in patients who have not previously received oxaliplatin or irinotecan.
WH0 performance status 0-1.

## ICD-10 codes

Codes prefixed with C18-20.

## Regimen details

| Day | Drug | Dose | Route |
|---|---|---|---|
| 1 | Oxaliplatin | 85mg/m2 | IV infusion |
| 1 | Calcium folinate | 350mg | IV infusion |
| 1 | Irinotecan | 165mg/$m^2$ | IV infusion |
| 1-2 | Fluorouracil | 3200mg/$m^2$ | IV infusion over 48 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. 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 advised on appropriate precautions to take. This does not require treatment or dose reduction but subsequent infusions should be given over 6 hours.

Calcium folinate is administered in 250-500mL sodium chloride 0.9% or glucose 5% over 2 hours.

Irinotecan is administered in 250mL sodium chloride 0.9% over 30 – 90 minutes. The first dose must be administered over 90 minutes. If this is well tolerated subsequent doses may be administered over 30 minutes.

Fluorouracil infusion is administered either via a central venous catheter and ambulatory infusion device over 48 hours or as a continuous peripheral IV infusion over 48 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.

Atropine 250 microgram SC should be administered 30 minutes prior to irinotecan to control anticholinergic syndrome. An additional dose may be given if this develops.

## Emetogenicity

This regimen has a high emetogenic potential

## Additional supportive medication

Mouthwashes as per local policy.
Loperamide if required.
Ciprofloxacin 250 mg BD for 5 days if diarrhoea persists for more than 24 hours.

Prophylactic ciprofloxacin should also be commenced in patients with neutrophils <0.5 x $10^9$/L, even in the absence of diarrhoea. Patients who develop severe neutropenia are especially at risk of infection if they are also suffering from diarrhoea.

## 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 | 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 | ≥ 100 x $10^9$/L |
| WCC | ≥ 3.0 x $10^9$/L |
| Bilirubin | < 1.5 x ULN |
| AST/ALT | < 1.5 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 <100 x $10^9$/L. If there is > 1 week delay due to haematological toxicity reduce oxaliplatin dose to 60mg/$m^2$, irinotecan to 150mg/$m^2$ and fluorouracil dose to 80%. Consider use of GCSF as per local policy.

If platelets 10-49 x $10^9$/L reduce oxaliplatin dose to 60mg/$m^2$ (if second occurrence reduce oxaliplatin dose to 50mg/$m^2$). Consider dose reduction of irinotecan to 150mg/$m^2$ and fluorouracil to 80%.

If platelets < 10 x $10^9$/L reduce oxaliplatin dose to 50mg/$m^2$ (if second occurrence – discuss with consultant). Consider dose reduction of irinotecan to 150mg/$m^2$ and fluorouracil to 80%.

If febrile neutropenia (neutrophils < 0.5 x $10^9$/L and fever requiring IV antibiotics) – reduce all subsequent doses of fluorouracil to 50%, oxaliplatin dose to 55mg/$m^2$ and irinotecan dose to 120mg/$m^2$. Consider use of GCSF as per local policy.

- **Renal impairment**

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

- **Hepatic impairment**

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

**Diarrhoea:**

If diarrhoea from the previous cycle (even if not severe) has not resolved (without loperamide for at least 24 hours), by the time the next cycle is due, delay 1 week.

If resolved to < grade 2 within 2 weeks continue treatment with the following dose reductions:

| Diarrhoea severity | Oxaliplatin dose | Irinotecan dose | Fluorouracil dose |
|---|---|---|---|
| Grade 2 | 100% | 100% | 80% |
| Grade 3 | 60mg/m$^2$ | 150mg/m$^2$ | 50% |
| Grade 4 | Discontinue treatment | | |

If diarrhoea persists after 2 weeks discontinue treatment.

**Diarrhoea may be life-threatening and requires prompt, aggressive treatment:**

• Early diarrhoea or abdominal cramps occurring within the first 24 hours should be treated with atropine 0.3 - 1.2 mg IV or SC. DO NOT ADMINISTER LOPERAMIDE DURING THIS 24 HOUR PERIOD.

• Late diarrhoea (diarrhoea occurring >24 hours after treatment) must be treated with loperamide; 4mg at the first loose stool and then 2mg every 2 hours until diarrhoea-free for 12 hours after last loose stool (4 mg every 4 hours may be taken over night). Note: this dose is higher than recommended by the manufacturer. If diarrhoea persists for >24 hours ciprofloxacin 500 mg BD should be commenced. Loperamide must not be administered for more than 48 consecutive hours at these doses without appropriate medical supervision due to the risk of paralytic ileus.

**Stomatitis:**
Treatment should be delayed until resolved to ≤ grade 1 and then doses reduced as follows:

| Toxicity definition | Fluorouracil dose |
|---|---|
| Grade 2 | 80% |
| Grade 3 | 50% |
| Grade 4 | Discontinue or 50% (consultant decision) |

**Palmar-plantar erythema:**
Treat symptomatically and treatment should be delayed until ≤ grade 1. Reduce doses as follows:

| Toxicity definition | Fluorouracil dose |
|---|---|
| Grade 2 | 80% |
| Grade 3-4 | 50% |

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

- **Serious side effects**

Myelosuppression
Infertility
Ocular toxicity
Severe diarrhoea
Allergic reactions
Neuropathy
Interstitial pulmonary disease
Rhabdomyolysis
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**

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

- **Other side effects**

Transient cerebellar syndrome
Confusion

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

**Warfarin/coumarin anticoagulants:** Avoid use due to elevations in INR. Switch to low molecular weight heparin during treatment.

**Oxaliplatin**:
Avoid nephrotoxic agents as these may increase toxicity of oxaliplatin.
Aminoglycoside antibiotics- increased risk of ototoxicity with oxaliplatin.
Medication which cause QT interval prolongation: use with caution.

**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.
**Phenytoin** – may increase phenytoin levels, risk of toxicity.
**Metronidazole** – may increase plasma levels of Fluorouracil

## 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). Contraindicated 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


- Falcon et al. Phase III Trial of Infusional Fluorouracil, Leucovorin, Oxaliplatin, and Irinotecan (FOLFOXIRI) Compared With Infusional Fluorouracil, Leucovorin, and Irinotecan (FOLFIRI) As FirstLine Treatment for Metastatic Colorectal Cancer: The Gruppo Oncologico Nord Ovest. J. Clinical Oncology 2007;25;1670-1676
- Summary of Product Characteristics Irinotecan (Pfizer) accessed 10 October 2018 via www.medicines.org.uk
- Summary of Product Characteristics Oxaliplatin (Sanofi) accessed 10 October 2018 via www.medicines.org.uk
- Summary of Product Characteristics Fluorouracil (Hospira) accessed 10 October 2018 via www.medicines.org.uk



Written/reviewed by: Dr A Cox (Consultant Oncologist, RUH Bath NHS Trust), Dr S Falk (Consultant Oncologist, UHBristol NHS Trust), Dr S Gangadara (Consultant Oncologist, RUH Bath NHS Trust)

Checked by: Sarah Murdoch (Senior Oncology Pharmacist, SW Clinical Network)

Authorised by: Dr J Braybrooke (Consultant Oncologist, UHBristol NHS Trust, SW Clinical Network)


Date: October 2018