Modified FOLFIRINOX (Pancreas)

Indication
Adjuvant or neoadjuvant treatment of pancreatic cancer.

Note: an alternative regimen is used for metastatic pancreatic cancer – see FOLFIRINOX protocol.

ICD-10 codes
Codes prefixed with C25

Regimen details

Day	Drug	Dose	Route
1	Calcium folinate	350mg	IV infusion
1	Oxaliplatin	85mg/m^2	IV infusion
1	Irinotecan	150mg/m^2	IV infusion
1-2 (46 hours)	Fluorouracil	2400mg/m^2	IV infusion over 46 hours

Cycle frequency
14 days

Number of cycles
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 advised on precautions to be taken. This does not require treatment or dose reduction but subsequent infusions should be given over 6 hours.

Irinotecan is administered in 250mL sodium chloride 0.9% over 90 minutes for the first dose then reduced to 30 minutes if no infusion related reactions.
Fluorouracil 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

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

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

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.
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
GCSF as per local policy

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** (or as per local policy)
FBC	14 days
U+E (including creatinine)	14 days
LFTs	14 days
Magnesium	14 days
DPD status	Pre-treatment

Investigations – pre subsequent cycles

Investigation	**Validity period** (or as per local policy)
FBC	96 hours
U+E (including creatinine)	7 days
LFTs	7 days
Magnesium	7 days

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
Platelets	≥ 100 x 10^9/L
Bilirubin	< 1.5 x ULN
ALT/AST	< 1.5 x ULN
Creatinine Clearance (CrCl)	≥ 50mL/min

Dose modifications

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 or dose reduce according to DPD levels in patients with known DPD deficiency.

- **Haematological toxicity**

Defer treatment for 1 - 2 weeks if neutrophil count <1.5 x 10^9/L and/or platelets <100 x 10^9/L. Repeat FBC and once recovered resume treatment as per the following table:

Toxicity	Occurrence	Irinotecan dose	Oxaliplatin dose	Fluorouracil dose
Neutrophils <1.5 x 10^9/L, febrile neutropenia* or neutrophils <0.5 x 10^9/L for > 7 days	1st	120mg/m^2	100%	1800mg/m2
	2nd	120mg/m^2	60mg/m^2	1800mg/m2
	3rd	Stop treatment		
Platelets <100 x 10^9/L	1st	Maintain full dose (150mg/m2)	60mg/m^2	100%
	2nd	120mg/m^2	60mg/m^2	1800mg/m2
	3rd	Stop treatment		

- **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

NB. Bilirubin > 3 x ULN: Note that significantly impaired hepatic function may be a sign of disease recurrence 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.

For subsequent cycles reduce dose as per the following table:

Toxicity	Occurrence	Irinotecan dose	Oxaliplatin dose	Fluorouracil dose
Grade 3-4 diarrhoea +/- fever	1st	120mg/m^2	100%	100%
	2nd	120mg/m^2	60mg/m^2	1800mg/m^2
	3rd	Stop 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.

Neurological toxicity:
If neurological symptoms occur, use the following oxaliplatin dose adjustments:
- Symptoms lasting > 7 days and troublesome; reduce oxaliplatin dose to 60mg/m^2
- Paraesthesia without functional impairment persisting until next cycle; reduce oxaliplatin dose to 60mg/m^2
- Paraesthesia with functional impairment persisting until the next cycle; oxaliplatin should be discontinued

Stomatitis:
If mouth ulcers ≥ Grade 2 develop, reduce fluorouracil dose to 1800mg/m^2 for subsequent cycles unless further toxicity occurs.

Palmar-plantar erythema:
Treat symptomatically.
If Grade 3-4 reduce fluorouracil to 1800mg/m^2 for subsequent cycles.

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

- **Serious side effects**

Myelosuppression
Neutropenic sepsis
Infertility
Allergic reactions
Neurotoxicity
Severe diarrhoea
Coronary artery spasm*

- **Frequently occurring side effects**

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

Alopecia
Fatigue
Dyspnoea

- **Other side effects**

*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, after discussion with consultant, re-challenge is deemed necessary, this can be performed under close supervision, for example as in in-patient with cardiac monitoring. If symptoms re-develop, the fluorouracil should be permanently discontinued.

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

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.

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 or DOAC 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/m^2. It can occur after treatment with oxaliplatin is completed, and is usually reversible, taking approximately 3 – 5 months to recovery.

References

- Summary of Product Characteristics Irinotecan (Pfizer) accessed 2 December 2021 via www.medicines.org.uk
- Summary of Product Characteristics Oxaliplatin (Sanofi) accessed 2 December 2021 via www.medicines.org.uk
- Summary of Product Characteristics Fluorouracil (Hospira) accessed 2 December 2021 via www.medicines.org.uk
- Conroy T et al; FOLFIRINOX or Gemcitabine as Adjuvant Therapy for Pancreatic Cancer NEJM 2018; 379: 2395 – 2406

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