



## FOLFIRINOX (pancreas)

### Indication

First or second line chemotherapy for metastatic pancreatic cancer.

Eligible patients must be <75 years, WHO performance status 0-1 and with a normal serum bilirubin.

### ICD-10 codes

Codes prefixed with C25

### Regimen details

Day	Drug	Dose	Route
1	Calcium folinate	350mg	IV infusion
1	Oxaliplatin	85mg/m <sup>2</sup>	IV infusion
1	Irinotecan	180mg/m <sup>2</sup>	IV infusion
1	Fluorouracil	400mg/m <sup>2</sup>	IV bolus
1-2 (46 hours)	Fluorouracil	2400mg/m <sup>2</sup>	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.

Irinotecan is administered in 250mL sodium chloride 0.9% over 30 – 90 minutes.

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

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 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 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  $<0.5 \times 10^9/L$ , 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

**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). Patients require DPD testing prior to administration. Dose adjustments should be made in accordance with local DPD policy.**

Investigation	Validity period (or as per local policy)
FBC	14 days
U+E (including creatinine)	14 days
LFTs	14 days
Magnesium	14 days

### Investigations – pre subsequent cycles

Investigation	Validity period (or as per local policy)
FBC	48 hours
U+E (including creatinine)	48 hours
LFTs	48 hours
Magnesium	48 hours
Ca19-9	48 hours



## 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	$\geq 1.5 \times 10^9/L$
Platelets	$\geq 100 \times 10^9/L$
Bilirubin	$< 1.5 \times \text{ULN}$
Alkaline phosphatase	$< 5 \times \text{ULN}$
Creatinine Clearance (CrCl)	$\geq 50\text{mL/min}$

## Dose modifications

### • Haematological toxicity

Defer treatment for 1 - 2 weeks if neutrophil count  $< 1.5 \times 10^9/L$  and/or platelets  $< 75 \times 10^9/L$ . Repeat FBC and once recovered resume treatment as per the following table:

Toxicity	Occurrence	Irinotecan dose	Oxaliplatin dose	Fluorouracil dose
Neutrophils $< 1.5 \times 10^9/L$ , febrile neutropenia* or neutrophils $< 0.5 \times 10^9/L$ for > 7 days	1 <sup>st</sup>	150mg/m <sup>2</sup>	100%	Omit bolus
	2 <sup>nd</sup>	150mg/m <sup>2</sup>	60mg/m <sup>2</sup>	Omit bolus
	3 <sup>rd</sup>	Stop treatment		
Platelets $< 100 \times 10^9/L$	1 <sup>st</sup>		60mg/m <sup>2</sup>	Reduce bolus and infusion to 75% dose
	2 <sup>nd</sup>	150mg/m <sup>2</sup>	60mg/m <sup>2</sup>	Reduce bolus and infusion to 75% dose
	3 <sup>rd</sup>	Stop treatment		

\* For febrile neutropenia or a 2<sup>nd</sup> episode of low neutrophils, G-CSF prophylaxis should be initiated with subsequent cycles (as per local policy)

### • Renal impairment

CrCl (mL/min)	Irinotecan dose	Oxaliplatin dose	Fluorouracil dose
GFR (ml/min)	Irinotecan	Oxaliplatin	5-FU
>50	Full	Full	Full
30-49	50% Dose	Full	80% dose
<30	Regimen may not be appropriate		

### • Hepatic impairment

Liver abnormality	Irinotecan dose	Oxaliplatin dose	Fluorouracil dose
Bilirubin 1.5-3 x ULN or Alkaline Phosphatase > 5 x ULN	50%	100%	Reduce bolus and infusion to 50-75% dose
Bilirubin* > 3 x ULN	omit	50%	Omit

\* Bilirubin > 3 x ULN: 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.

For subsequent cycles reduce dose as per the following table:

Toxicity	Occurrence	Irinotecan dose	Oxaliplatin dose	Fluorouracil dose
Grade 3-4 diarrhoea +/- fever	1 <sup>st</sup>	150mg/m <sup>2</sup>	100%	Omit bolus
	2 <sup>nd</sup>	150mg/m <sup>2</sup>	60mg/m <sup>2</sup>	Omit bolus and reduce infusion to 75% dose
	3 <sup>rd</sup>	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:**

Toxicity	Duration of toxicity 1-7 days	Duration of toxicity >7 days	Persistent between cycles
Cold-related dysaesthesia	No reduction	No reduction	Withhold oxaliplatin until recovery then restart at 60mg/m <sup>2</sup>  Omit oxaliplatin if recurs
Paraesthesia without pain	No reduction	No reduction	Withhold oxaliplatin until recovery then restart at 60mg/m <sup>2</sup>  Omit oxaliplatin if recurs
Paraesthesia with pain or functional impairment	No reduction	Reduce to 60mg/m <sup>2</sup> on subsequent cycles  Omit oxaliplatin if recurs	Omit oxaliplatin Discuss with consultant
Acute laryngopharyngeal dysaesthesia	Increase infusion duration to 6 hrs.		

**Stomatitis:**

If mouth ulcers ≥ Grade 2 develop, reduce fluorouracil doses (bolus and infusion) to 75% dose for subsequent cycles unless further toxicity occurs.

**Palmar-plantar erythema:**

Treat symptomatically.

If Grade 3-4 reduce fluorouracil bolus and infusion to 75% dose 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 re-challenge is deemed necessary, this can be performed under close supervision, but should symptoms redevelop, 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 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/m<sup>2</sup>. It can occur after treatment with oxaliplatin is completed, and is usually reversible, taking approximately 3 – 5 months to recovery.

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## References

- <http://www.swscn.org.uk/guidance-protocols/cancer-protocols/> accessed 9 Jul 2020
- Conroy T et al; NEJM 2011; 364: 1817 – 1825
- Summary of Product Characteristics Irinotecan via [www.medicines.org.uk](http://www.medicines.org.uk)
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- Summary of Product Characteristics Fluorouracil via [www.medicines.org.uk](http://www.medicines.org.uk)
- Allwood M, Stanley A, Wright P, editors. The cytotoxics handbook. 4<sup>th</sup> ed. Radcliffe Medical Press. 2002.

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**THIS PROTOCOL HAS BEEN DIRECTED BY DR MITCHELL, DESIGNATED LEAD CLINICIAN FOR UPPER GI CANCER**

**RESPONSIBILITY FOR THIS PROTOCOL LIES WITH THE HEAD OF SERVICE**

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