Chemotherapy Protocol

PANCREATIC CANCER

FLUOROURACIL-FOLINIC ACID-IRINOTECAN-OXALIPLATIN

(FOLFIRINOX)

This protocol may require funding

Regimen

- Pancreatic Cancer - Fluorouracil-Folinic Acid-Irinotecan-Oxaliplatin (FOLFIRINOX)

Indication

- Advanced / metastatic pancreatic cancer that has progressed following adjuvant gemcitabine
- WHO performance status 0, 1
- Palliative intent.

Toxicity

Drug	Adverse Effect
Fluorouracil	Palmar-plantar erythrodysesthesia, diarrhoea, chest pain, mucositis
Irinotecan	Acute cholinergic syndrome, diarrhoea (may be delayed)
Oxaliplatin	Peripheral neuropathy (cumulative), acute laryngopharyngeal dysasthesia (increase duration of infusion)

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

Monitoring

Drugs

- FBC, LFTs and U&Es prior to day each cycle
- Patients with complete or partial dihydropyrimidine dehydrogenase (DPD) deficiency are at increased risk of severe and fatal toxicity during treatment with fluorouracil. All patients should be tested for DPD deficiency before initiation (cycle 1) to minimise the risk of these reactions

Dose Modifications

The dose modifications listed are for haematological, liver and renal function and drug specific toxicities only. Dose adjustments may be necessary for other toxicities as well.

In principle all dose reductions due to adverse drug reactions should not be re-escalated in subsequent cycles without consultant approval. It is also a general rule for chemotherapy that if a third dose reduction is necessary treatment should be stopped.

Please discuss all dose reductions / delays with the relevant consultant before prescribing, if appropriate. The approach may be different depending on the clinical circumstances.

Haematological

Consider a blood transfusion if patient symptomatic of anaemia or has a haemoglobin of less than 8g/dL.

Prior to cycle one the following criteria must be met

Criteria	Eligible Level
Neutrophil	equal to or more than 1.5 x10^9/L
Platelets	equal to or more than 100 x10^9/L

Thereafter the following tables apply:.

Neutrophils (x10^9/L)	Occurrence	Dose Modifications		
		Fluorouracil	Irinotecan	Oxaliplatin
1.5 or greater	N/A	100%	100%	100%
less than 1.5 on day 1 or at any time since the previous cycle: - febrile neutropenia - NCI-CTC grade 3/4 infection - NCI-CTC grade 4 neutropenia for more than 7 days	1st	omit bolus dose	150mg/m^2	100%
	2nd	omit bolus dose	150mg/m^2	60mg/m^2
	3rd	stop treatment	stop treatment	stop treatment

Platelets (x10^9/L)	Occurrence	Dose Modifications		
		Fluorouracil	Irinotecan	Oxaliplatin
75 or greater	N/A	100%	100%	100%
less than 75 on day 1 or a NCI-CTC grade 3/4 thrombocytopenia since the previous cycle	1st	75%	100%	60mg/m^2
	2nd	75%	150mg/m^2	60mg/m^2
	3rd	stop treatment	stop treatment	stop treatment

If counts have not recovered after a delay of two weeks, despite appropriate supportive measures, it is recommended that treatment is stopped.

There is no need to dose adjust the folinic acid dose for haematological counts. However, folinic acid should be omitted if the fluorouracil is omitted.

Hepatic Impairment

Drug	Bilirubin µmol/L		Child Pugh	Dose (% of original dose)
Fluorouracil			A	100%
			B	67% *
			C	50% *
Irinotecan	35 - 50			75%
	more than 50			50%
Oxaliplatin			A/B	100%
			C	Clinical decision

* The dose of fluorouracil may be increased according to tolerability

Renal Impairment

Drug	Creatinine Clearance (ml/min)	Dose (% of original dose)
Fluorouracil	N/A	No dose modification needed
Irinotecan	N/A	Dose modifications not thought necessary although limited data in this setting
Oxaliplatin	less than 20	contra-indicated

Other

Dose reductions or interruptions in therapy are not necessary for those toxicities that are considered unlikely to be serious or life threatening. For example, alopecia, altered taste or nail changes.

For all other non-haematological NCI-CTC grade 3 and above toxicities delay treatment until the adverse effect has resolved to NCI-CTC grade 1 or below. The dose of the causative agent should then be reduced (fluorouracil to 75% of the original dose, irinotecan to 150mg/m^2, oxaliplatin to 60mg/m^2) or discontinued as appropriate. The following guidance applies in specific cases.

Diarrhoea

NCI-CTC grade 1 or 2 diarrhoea occurring between cycles does not generally necessitate dose modification, unless accompanied by fever or neutropenia. However, diarrhoea should have completely resolved before re-treatment, especially with irinotecan. If the diarrhoea has not fully resolved delay treatment by seven days and reassess.

The following dose modifications below should be applied to subsequent cycles where appropriate:

Diarrhoea	**Occurrence**	**Dose Modifications (% of the original dose)**		
		Fluorouracil	**Irinotecan**	**Oxaliplatin**
At any time since the previous cycle: - NCI-CTC grade 3/4 - accompanied by fever and / or NCI-CTC grade 3/4 neutropenia	1st	omit bolus dose	150mg/m^2	100%
	2nd	omit bolus dose and reduce the dose of the continuous infusion to 75%	150mg/m^2	60mg/m^2
	3rd	stop treatment	stop treatment	stop treatment

Fluorouracil

Where a NCI-CTC Grade 3 or 4 stomatitis occurs reduce the fluorouracil bolus and infusion doses to 75% of the original dose.

For a NCI-CTC Grade 3 or 4 palmer-plantar erythrodysesthesia reduce the fluorouracil bolus and infusion doses to 75% of the original dose.

Fluorouracil should be stopped in any case of angina pectoris or of myocardial infarction.

Oxaliplatin

If the neurosensory toxicity is NCI-CTC Grade 1 or 2 and lasts less than seven days administer the full dose of oxaliplatin. If the toxicity is NCI-CTC Grade 2 and persists for more than seven days reduce the oxaliplatin dose to 60mg/m^2. Oxaliplatin should be discontinued for neurosensory toxicities NCI-CTC grade 3 or above.

For transient cold related dysaesthesia or paresthesia without pain there is no need to delay or reduce oxaliplatin.

For acute laryngopharygeal dysaesthesia increase the infusion time to six hours.

There are rare case reports of acute interstitial lung disease or lung fibrosis in association with oxaliplatin. Where an unexplained respiratory symptoms occur stop treatment until pulmonary investigations have been conducted to exclude an interstitial cause.

Regimen

14 day cycle for 12 cycles

Drug	Dose	Days	Administration
Fluorouracil	400mg/m^2	1	Intravenous bolus
Fluorouracil	2400mg/m^2	1	Intravenous infusion over 46 hours
Folinic Acid	350mg	1	Intravenous infusion in 250ml glucose 5% over 120 minutes
Oxaliplatin	85mg/m^2	1	Intravenous infusion in 500ml glucose 5% over 120 minutes
Irinotecan	180mg/m^2	1	Intravenous infusion in 250ml sodium chloride 0.9% over 90 minutes

Dose Information

- Fluorouracil will be dose banded in accordance with the national dose bands (25mg/ml PM bolus and 50mg/ml infusion)
- Irinotecan will be dose banded in accordance with the national dose bands (20mg/ml)
- Oxaliplatin will be dose banded in accordance with the national dose bands (5mg/ml)

Administration Information

Extravasation

- Fluorouracil - inflammitant
- Irinotecan - irritant
- Oxaliplatin - exfoliant

Other

- Central venous access and use of an ambulatory infusion pump is required
- A glucose 5% flush should be administered before and after the oxaliplatin

Additional Therapy

- Antiemetics

  15-30 minutes prior to chemotherapy

  - dexamethasone 8mg oral or intravenous
  - ondansetron 8mg oral or intravenous

  As take home medication

  - dexamethasone 4mg oral twice a day for 3 days
  - metoclopramide 10mg oral three times a day as required
  - ondansetron 8mg oral twice a day for 3 days

- Subcutaneous atropine 0.25mg immediately prior to irinotecan and then when required for the relief of acute cholinergic syndrome.

- Oral loperamide 2mg every two hours once first liquid stool appears and continue until 12 hours after the last liquid stool. Do not use for longer than 48 hours.

- Consider oral ciprofloxacin 500mg twice daily where diarrhoea continues for more than 24 hours. Review the patient before starting this treatment.

- Mouthwashes as per national or local guidelines for the treatment of mucositis

- Gastric protection with a proton pump inhibitor or a H_2 antagonist may be considered in patients considered at high risk of GI ulceration or bleed.

Additional Information

- The folinic acid may be replaced with calcium levofolinate 175mg intravenous infusion in 250ml glucose 5% over 120 minutes

References

Conroy T, Desseigne F, Ychou M et al. FOLFIRINOX versus Gemcitabine for Metastatic Pancreatic Cancer. N Engl J Med 2011; 364:1817-1825.

REGIMEN SUMMARY

Fluorouracil-Folinic Acid-Irinotecan-Oxaliplatin (FOLFIRINOX)

Day One

1. Dexamethasone 8mg oral or intravenous
2. Ondansetron 8mg oral or intravenous
3. Oxaliplatin 85mg/m^2 in 500ml glucose 5% intravenous infusion over 120 minutes
4. Atropine Sulphate 250mcg subcutaneous for the prevention of irinotecan associated cholinergic symptoms.
5. Irinotecan 180mg/m^2 in 250ml sodium chloride 0.9% intravenous infusion over 90 minutes.
6. Folinic Acid 350mg in 250ml glucose 5% intravenous infusion over 120 minutes
7. Fluorouracil 400mg/m^2 intravenous bolus over 10 minutes
8. Fluorouracil 2400mg/m^2 intravenous infusion over 46 hours
9. Atropine 250microgram subcutaneous when required for the treatment of irinotecan associated cholinergic symptoms

Take Home Medicines

10. Dexamethasone 4mg oral twice a day for 3 days starting on day 2 of the cycle
11. Metoclopramide 10mg oral three times a day when required for nausea
12. Ondansetron 8mg oral twice a day for 3 days starting on the evening of day 1 of the cycle

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1.2	Nov 2020	Updated monitoring with DPD testing Dose banding updated Coding removed	Donna Kimber Pharmacy Technician	Rebecca Wills Pharmacist
2	July 2014	Header changed Bolus removed from supportive therapies OPCS codes updated Atropine added prior to irinotecan Irinotecan administration changed to 90 minutes TTOs clarified Disclaimer added		
1	March 2012	None	Rebecca Wills Pharmacist Dr Debbie Wright Pharmacist	Dr Tim Iveson Consultant Medical Oncologist

This chemotherapy protocol has been developed as part of the chemotherapy electronic prescribing project. This was and remains a collaborative project that originated from the former CSCCN. These documents have been approved on behalf of the following Trusts;

Hampshire Hospitals NHS Foundation Trust
NHS Isle of Wight
Portsmouth Hospitals NHS Trust
Salisbury NHS Foundation Trust
University Hospital Southampton NHS Foundation Trust
Western Sussex Hospitals NHS Foundation Trust

All actions have been taken to ensure these protocols are correct. However, no responsibility can be taken for errors which occur as a result of following these guidelines.