FOLFIRINOX (Irinotecan, Oxaliplatin & infusional Fluorouracil)

NHS Northern Cancer Alliance

DRUG ADMINISTRATION SCHEDULE

Day	Drug	Dose	Route	Diluent & Rate
Day 1	Glucose 5%	500ml	Infusion	Fast Running for Line Flush
	Ondansetron	8mg	Oral	
	Dexamethasone	8mg	Oral /Slow bolus/15 min infusion	
	Oxaliplatin	**85 mg/m²**	IV infusion	250ml Glucose 5% over 2 hours
	Calcium Folinate (Folinic Acid)	**200 mg/m²**	IV Infusion	250ml Glucose 5% over 2 hours. After 30minutes start Irinotecan
	Irinotecan	**180mg/m²**	IV Infusion	Over 90 minutes in 250ml Glucose 5% alongside folinic acid
	Glucose 5%			250ml Line Flush
	5 Fluorouracil	**400 mg/m²**	IV bolus	Over 5 minutes
	5 Fluorouracil	**2400 mg/m²**	via infusor device	Sodium Chloride 0.9% over **46 hours**
Day 3	Attend ward/clinic for removal of 5-FU infusor device			

*Ondansetron IV must be infused over 15 minutes in patients over 65 years of age.

CYCLE LENGTH AND NUMBER OF DAYS
Every 14 days for a maximum of 12 cycles

APPROVED INDICATIONS
First line for inoperable pancreatic cancer in patients with performance status 0 or 1

PREMEDICATION
***If acute cholinergic syndrome appears atropine sulphate 250-300 micrograms should be administered by subcutaneous injection unless clinically contraindicated**.
The manufacturer recommends the use of prophylactic atropine sulphate with subsequent doses of irinotecan.

RECOMMENDED TAKE HOME MEDICATION
Ondansetron 8mg twice daily for 2 to 3 days
Dexamethasone 4mg twice daily for 1 to 3 days
Metoclopramide 10mg three times daily as required
Loperamide as required (4mg after first loose stool and 2mgs every 2 hours, to a maximum of 16 (2mg) tablets in 24 hours.
Suggested antiemetic regimen - may vary with local practice. See CINV policy for more details

INVESTIGATIONS / MONITORING REQUIRED
Blood Pressure ½ hourly during and post administration of irinotecan for ½ hour
FBC, U&Es, LFTs & tumour markers as appropriate prior to each course of chemotherapy.
Where CEA is elevated this should be measured before each cycle.

ASSESSMENT OF RESPONSE

Assessed radiologically after 4th cycle.
Metastatic: Tumour size and patient symptomatic response

REVIEW BY CLINICIAN

To be reviewed by either a Nurse, Pharmacist or Clinician before every cycle.

NURSE / PHARMACIST LED REVIEW

On cycles where not seen by clinician.

ADMINISTRATION NOTES

- Irinotecan must only be given in units where clear arrangements are made to manage possible toxicity related out of hour's admissions. Patients must be made aware of the risk of delayed diarrhoea occurring 24 hours after the administration of Irinotecan and at any time before the next cycle. This means supplying information sheets to the patient and if appropriate to their GP.
- Early onset diarrhoea (within the first 24 hours) can be a result of acute cholinergic syndrome and may occur in 9% of patients. Symptoms are short lasting and respond within minutes to administration of atropine (0.25-1mg subcutaneously)
- Delayed diarrhoea must be treated immediately with high dose Loperamide (4mg after first loose stool and 2mg every 2 hours, to a maximum of 16 (2mg) tablets in 24 hours. Hospitalise if condition not resolved in 48 hours.
- For diarrhoea lasting greater than 24 hours add ciprofloxacin 250mg BD. *Note* some units give patient a supply of loperamide and ciprofloxacin at the start of treatment.
- Two forms of Folinic Acid are available. The doses given above refer to 'standard' racemic calcium folinate only. If the pure active enantiomer, calcium levofolinate (Isovorin®) is used the dose will generally be half that of the 'standard' folinate.
- Patients receiving oxaliplatin should avoid cold drinks and must not use ice chips to reduce the risk of mucositis. Care should be taken to avoid exposure to cold air especially on the day of treatment.

Platinum hypersensitivity can cause dyspnoea, bronchospasm, itching and hypoxia. Appropriate treatment includes supplemental oxygen, steroids, epinephrine and bronchodilators. Vasopressors may be required. (see below)

Patients who have previously experienced Grade I or II Platinum Hypersensitivity should be pre-medicated with:
45 minutes prior to Oxaliplatin:

- Dexamethasone 20 mg IV in 50 mL NS over 15 minutes (or Hydrocortisone 100mg)

30 minutes prior to Oxaliplatin:

- Chlorphenamine 10 mg IV and Ranitidine 50 mg IV in 50 mL NS over 20 minutes

Laryngo-pharyngeal dysesthesia is an unusual dysesthesia characterized by a loss of sensation of breathing without any objective evidence of respiratory distress (hypoxia, laryngospasm or bronchospasm). This may be exacerbated by exposure to cold air. If this occurs during infusion, stop infusion immediately and observe patient. Rapid resolution is typical, within minutes to a few hours. Check oxygen saturation; if normal, an anxiolytic agent may be given. The infusion can then be restarted at a slower rate at the physician's discretion. In subsequent cycles, the duration of infusion should be prolonged (to 6 hours).

Clinical Symptoms	Laryngo-pharyngeal Dysesthesia	Platinum Hypersensitivity
Dyspnoea	Present	Present
Bronchospasm	Absent	Present
Laryngospasm	Absent	Present
Anxiety	Present	Present
O2 Saturation	Normal	Decreased
Difficulty Swallowing	Present (loss of sensation)	Absent
Pruritis	Absent	Present
Cold induced symptoms	Yes	No
Blood pressure	Normal or increased	Normal or Decreased
Treatment	Anxiolytics; observation in a controlled clinical setting until symptoms abate or at physician's discretion	Oxygen, steroids, adrenaline, bronchodilators; Fluids and vasopressors if appropriate

EXTRAVASATION *See NCA / local Policy*

TOXICITIES

- Acute cholinergic syndrome (defined as early diarrhoea and various other symptoms such as sweating, abdominal cramping, lacrimation, miosis and salivation)
- Diarrhoea –risk of severe delayed diarrhoea – can be life threatening
- Peripheral neurotoxicity very common with Oxaliplatin. (dose limiting toxicity)
- Myelosuppression
- Alopecia
- Dizziness during treatment
- Anaphylaxis
- Nausea and Vomiting
- Allergic reaction
- Stomatitis
- Palmar/Plantar Erythrodysesthesia
- Darkening/discoloration of veins
- Cardiotoxicity - Occasionally patients may experience coronary artery spasm
- Laryngopharyngeal dysesthesia

DOSE MODIFICATION / TREATMENT DELAYS

Haematological toxicity:

FBC on day 1			Treatment Delay	Dose reduction			
ANC		**PLT**		Episode	Irinotecan	Oxaliplatin	Folinic Acid & Fluorouracil
≥ 1.5	and	≥ 75	No delay		No reduction	No reduction	No reduction
1.0 – 1.49		-	Delay until ANC ≥ 1.5 (If delay > 14days discontinue)	1st	Reduce to 150mg/m²	No reduction	Reduce 5Fu bolus & infusion 20%
				2nd	Stay at 150mg/m²	Reduce to 65mg/m²	Stop 5Fu bolus & Folinic Acid.
				3rd	Stop	Stop	Stop
0.5 –0.99			Delay until ANC ≥ 1.5 (If delay > 14days discontinue)	1st	Reduce to 150mg/m²	No reduction	Stop 5Fu bolus & Folinic Acid. Reduce 5Fu infusion dose 20%
				2nd	Reduce to 120mg/m²	Reduce to 65mg/m²	No further reduction
				3rd	Stop	Stop	Stop
< 0.5			Delay until ANC ≥ 1.5 (If delay > 14days discontinue)	1st	Reduce to 150mg/m²	Reduce to 65mg/m²	Stop 5Fu bolus & Folinic Acid. Reduce 5Fu infusion dose 20%
				2nd	Reduce to 120mg/m²	Reduce to 50mg/m²	No further reduction
				3rd	Stop	Stop	Stop
		50 - 74	Delay until PLT ≥ 75 (If delay > 14days discontinue)	1st	No reduction	Reduce to 65mg/m²	Reduce 5Fu bolus & infusion 20%
				2nd	Reduce to 150mg/m²	Maintain reduced dose	Stop 5Fu bolus & Folinic Acid.
				3rd	Stop	Stop	Stop
		< 50	Delay until PLT ≥ 75 (If delay > 14days discontinue)	1st	No reduction	Reduce to 65mg/m²	Reduce 5Fu bolus & infusion 20%
				2nd	Reduce to 150mg/m²	Reduce to 50mg/m²	Stop 5Fu bolus & Folinic Acid.
				3rd	Stop	Stop	Stop

Oxaliplatin Neurologic Toxicity:

Neurologic Toxicity (CTC Grade)	Duration of toxicity		Present at start of next cycle
	≤ 7 days	> 7 days	
Grade 1	No reduction	No reduction	No reduction
Grade 2	No reduction	No reduction	Reduce to 65mg/m²
Grade 3	1st Episode: 65mg/m² 2nd Episode: 50mg/m²	1st Episode: 65mg/m² 2nd Episode: 50mg/m²	Stop
Grade 4	Stop	Stop	Stop
Pharyngo-laryngeal	No change required	Increase oxaliplatin infusion to 6 hours	Increase oxaliplatin infusion to 6 hours

Non-haematological, non-neurologic toxicity:

Diarrhoea CTC Grade (worst experienced)	Treatment Delay	Dose Reduction		
		Irinotecan	Oxaliplatin	Folinic Acid & Fluorouracil
Grade 1	No delay	No reduction	No reduction	No reduction
Grade 2	Delay until Grade 1 or better. If delay > 2 weeks stop treatment	No reduction	No reduction	No reduction
Grade 3		Reduce to: 150mg/m²	No reduction	Stop 5Fu bolus & Folinic Acid. Reduce 5Fu infusion 20%.
Grade 4		Stop	Reduce to 65mg/m²	Stop 5Fu bolus & Folinic Acid. Reduce 5Fu infusion 20%.

Stomatitis CTC Grade (worst experienced)	Treatment Delay	Dose Reduction		
		Irinotecan	Oxaliplatin	Folinic Acid & Fluorouracil
Grade 1	No delay	No reduction	No reduction	No reduction
Grade 2	Delay until Grade 1 or better. If delay > 2 weeks stop treatment	No reduction	No reduction	No reduction
Grade 3		No reduction	No reduction	Reduce 5Fu bolus & 5Fu infusion 20%.
Grade 4		Reduce to 150mg/m²	Reduce to 65mg/m²	Stop 5Fu bolus & Folinic Acid. Reduce 5Fu infusion 20%.

HEPATIC & RENAL IMPAIRMENT

Patients with significant hepatic and renal function impairment should not normally commence on this treatment. For patients who develop renal or hepatic impairment on treatment a reduction may be appropriate:

- IF ALT > 3ULN DO NOT GIVE and consult with prescriber before proceeding
- Bilirubin rising consider 50% dose reduction of irinotecan in the absence of firm data to confirm safety. Omit irinotecan if Bilirubin 3 x ULN.
- Oxaliplatin and Irinotecan are both renally excreted. In the absence of firm data to confirm safety for GFR < 30ml/min, consider 50% dose reduction, or use of alternative treatment.

TREATMENT LOCATION

Can be given at Cancer Centre or Cancer Unit. Patients need to be adequately warned about the risk of neutropenia and diarrhoea.

REFERENCE

1. Conroy, Thierry, et al. "FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer." New England Journal of Medicine 364.19 (2011): 1817-1825.

Document Control

Document Title:	FOLFIRINOX (Irinotecan, Oxaliplatin & infusional Fluorouracil)		
Document No:	CRP11 UG014	**Current Version:**	1.2
Reviewer:	Chris Beck –Chemo Pharmacist NCA	**Date Approved:**	09.03.2018
Approved by:	Steve Williamson Consultant Pharmacist Northern Cancer Alliance	**Due for Review:**	09.03.2021
Summary of Changes	1.1	Reformatted to CNTW format	
	1.2	Updated against Chemocare protocol & parameters	