Systemic Anti Cancer Therapy Protocol

FOLFIRINOX
Pancreatic Cancer

PROTOCOL REF: MPHAFOFINO
(Version No: 2.1)

Approved for use in

First line treatment of metastatic adenocarcinoma of pancreas.

For patients with ECOG PS 0-1 and normal hepatic and renal function.

Dosage

Drug	Dose	Route	Frequency
Oxaliplatin	85mg/m^2	IV	Day 1 of 14 day cycle
Folinic Acid	350mg	IV	Day 1 of 14 day cycle
Irinotecan	180mg/m^2	IV	Day 1 of 14 day cycle
Fluorouracil*	400mg/m^2	IV	Day 1 of 14 day cycle
Fluorouracil	2400mg/m^2	IV	Days 1 and 2 of 14 day cycle

Repeated every 14 days until disease progression

***Fluorouracil bolus injection is usually omitted to reduce risk of myelosuppression

Supportive Treatments:

Filgrastim s/c administered for 5 days starting on day 3 post chemotherapy

Dexamethasone tablets 4mg twice daily for 3 days

Domperidone 10mg oral tablets, up to 3 times a day or as required

Loperamide 4mg at onset then 2mg after each loose stool (max.16mg in 24hrs)

Thromboprophylaxis:

In line with recent NICE recommendations, patients with pancreatic cancer receiving chemotherapy should receive thromboprophylaxis with a LMWH unless contra-indicated. Contra-indications include high bleeding-risk. The decision regarding thromboprophylaxis as part of chemotherapy has to be clearly documented by the consultant.

- Dalteparin 5000 IU by subcutaneous injection once daily

Extravasation risk

Oxaliplatin EXFOLIANT – use heat and compression, consider hyaluronidase

Irinotecan IRRITANT – use cold pack and compression

Fluorouracil INFLAMMANT - use cold pack and compression

Refer to Clatterbridge Policy 'Prevention and Management of Extravasation Injuries' for further guidance.

Administration

Day	Drug	Dose	Route	Diluent and rate
1	**Ondansetron** 30mins before chemotherapy	**16mg**	**PO**	
	Dexamethasone 30mins before chemotherapy	**8mg**	**PO**	
	Oxaliplatin	**85mg/m^2**	**IV**	500mL Glucose 5% infusion over 2 hours
	Folinic Acid	**350mg**	**IV**	250mL Glucose 5% infusion over 2 hours
	Atropine	600micrograms	SC	Prior to Irinotecan
	Irinotecan	**180mg/m^2**	**IV**	250mL Glucose 5% infusion over 30 to 60 minutes
	Fluorouracil	**400mg/m^2**	**IV**	Bolus injection administered over 5 minutes
	Fluorouracil	**2400mg/m^2**	**IV**	Sodium chloride 0.9% over 46 hours via infusor device

Platinum hypersensitivity: can cause dyspnoea, bronchospasm itching and hypoxia. Appropriate treatment includes supplemental oxygen, steroids, epinephrine and bronchodilators.

Grade 1 or 2 hypersensitivity reactions do not require dose modification of oxaliplatin and patients may continue with hypersensitivity premedication:

- 45 minutes prior to Oxaliplatin – dexamethasone 20mg IV in 50mL Sodium Chloride 0.9% over 15 minutes
- 30 minutes prior to Oxaliplatin – chlorphenamine 10mg IV and ranitidine 50mg IV in 50mL Sodium Chloride 0.9% over 20 minutes (compatible up to 3 hours when mixed in bag)

Laryngo-pharyngeal dysaesthesia: characterised by loss of sensation of breathing without any objective evidence of distress (hypoxia, laryngospasm or bronchospasm). May be exacerbated by cold air. If this occurs during the infusion, stop the infusion immediately and observe the patient. Resolution is relatively rapid (within minutes to a few hours). Check oxygen saturation; if normal an anxiolytic agent may be given. The infusion can be restarted at a slower rate at the clinicians' discretion.

For subsequent cycles the duration should be prolonged (4-6 hours).

Clinical Symptoms	Laryngo-pharyngeal Dysaesthesia	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
Pruritus	Absent	Present
Cold-induced symptoms	Yes	No
Blood pressure	Normal or increased	Normal or decreased
Treatment	Anxiolytics; observe in a clinical setting until symptoms reduce or at clinician's discretion	Oxygen, steroids, adrenaline, bronchodilators; fluids and vasopressors if appropriate

Main Toxicities

Oxaliplatin
Nausea, vomiting, diarrhoea, constipation, neutropenia, thrombocytopenia, anaemia, alopecia. Liver function test abnormalities, hyperbilirubinaemia. Laryngo-pharyngeal dysaesthesia (dysphagia, dyspnoea, jaw spasm), paraesthesia. Allergic reaction (rash, urticaria), anaphylaxis.
Irinotecan
Nausea, vomiting, diarrhoea, neutropenia, thrombocytopenia, anaemia, alopecia. Liver function test abnormalities, hyperbilirubinaemia. Acute cholinergic syndrome (including diarrhoea, abdominal pain, hypotension, dizziness, malaise, increased salivation).
Fluorouracil
Diarrhoea, stomatitis, alopecia, palmer-plantar erythrodysesthesia (hand-foot syndrome). Chest pain, tachycardia.

Investigations and treatment plan:

	Pre	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Ongoing
Medical Assessment	X		X		X	For palliative, alternate cycles.
Nursing Assessment	X	X	X	X	X	Every cycle
FBC	X	X	X	X	X	Every cycle
U&E & LFT	X	X	X	X	X	Repeat if clinically indicated
Magnesium	X	X	X	X	X	Every cycle
Dihydropyrimidine dehydrogenase (DPD) deficiency test	X					This test is normally only required if a patient has not had capecitabine, or fluorouracil in the past. However a consultant may still request this test if capecitabine or fluorouracil was not tolerated previously. The result must be available before administration of chemotherapy unless clear documentation from the consultant is available to the contrary. Treatment with capecitabine and fluorouracil is contraindicated in patients with known complete DPD deficiency.
Random blood glucose	X	X	X	X	X	Every cycle
CA19.9	X	X	X	X	X	Every cycle
CT scan	X					Every 12 weeks
Informed Consent	X					
Blood pressure*	X					Repeat if clinically indicated
PS recorded	X	X	X	X	X	Every cycle
Toxicities documented	X	X	X	X	X	Every cycle
Weight recorded	X	X	X	X	X	Every cycle

Dose Modifications and Toxicity Management

Haematological Toxicity

FBC on Day 1			Treatment Delay	Dose Reduction			
ANC	AND	PLT		Episode	Irinotecan	Oxaliplatin	Fluorouracil
≥ 1.0		≥ 75	No delay		No reduction	No reduction	No reduction
< 1.0		-	Delay until ANC ≥ 1.0 (if delay > 14 days discontinue)	1st	Reduce to 150mg/m^2	No reduction	Omit bolus
				2nd	Continue at 150mg/m^2	Reduce to 60mg/m^2	Omit bolus and reduce infusor by 25%
				3rd	STOP	STOP	STOP
-		< 75	Delay until PLT ≥ 75 (if delay > 14 days discontinue)	1st	No reduction	Reduce to 60mg/m^2	Omit bolus
				2nd	Reduce to 150mg/m^2	Continue at 60mg/m^2	Omit bolus and reduce infusor by 25%
				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 60mg/m^2
Grade 3	1st: reduce to 60mg/m^2 2nd: reduce to 50mg/m^2	1st: reduce to 60mg/m^2 2nd: reduce to 50mg/m^2	STOP
Grade 4	STOP	STOP	STOP
Laryngo-pharyngeal spasm	No change required	Increase oxaliplatin infusion time to 6 hours	Increase oxaliplatin infusion time to 6 hours

Non-haematological, non-neurologic toxicity

Diarrhoea Toxicity (CTC Grade)	Treatment Delay	Dose Reduction		
		Irinotecan	Oxaliplatin	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/m^2	No reduction	Omit bolus and reduce infusor by 25%
Grade 4		STOP	Reduce to 60mg/m^2	Omit bolus and reduce infusor by 25%

Stomatitis Toxicity (CTC Grade)	Treatment Delay	Dose Reduction		
		Irinotecan	Oxaliplatin	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	Omit bolus and reduce infusor by 25%
Grade 4		Reduce to 150mg/m^2	Reduce to 60mg/m^2	Omit bolus and reduce infusor by 25%

Hepatic impairment

Oxaliplatin
Renally excreted therefore no dose adjustments necessary.
Irinotecan
Consider dose reduction if bilirubin > 26µmol/L. Not recommended in patients with bilirubin >51µmol/L.
Fluorouracil
Contra-indicated if bilirubin > 5x ULN.

Renal impairment

Oxaliplatin
Contra-indicated if CrCl < 30ml/min (no safety data). Consider dose reduction for patients with moderate renal impairment (< 60ml/min).
Irinotecan
Not recommended (not studied in patients with renal impairment).
Fluorouracil
Consider dose reduction in severe renal impairment (< 30ml/min).

References:

1. Conroy T et al; FOLFIRINOX versus Gemcitabine for Metastatic Pancreatic Cancer. NEJM 2011; 364: 1817-1825

2. Campto™ (Irinotecan) Concentrate for solution for infusion. Summary of Product Characteristics. Pfizer Limited, Kent 30/04/2013. Available from https://www.medicines.org.uk/emc last update 30/04/2013.

3. Fluorouracil 25 mg/ml injection. Summary of Product Characteristics. Hospira UK Ltd, Warwickshire 19/07/2004. Available from https://www.medicines.org.uk/emc last updated 24/09/14.

4. Oxaliplatin 5mg/ml Powder for Solution for Infusion. Summary of Product Characteristics. Accord Healthcare Ltd Middlesex 11/09/2008. Available from https://www.medicines.org.uk/emc last updated 08/02/2012.

5. Dosage Adjustment for Cytotoxics in Renal and Hepatic Impairment. University College London Hospital NHS Foundation Trust January 2009.

6. Cancer Chemotherapy: Guidelines for the administration of chemotherapy and the nursing care of cancer patients (6th Edition)

7. NICE guideline NG89. Venous thromboembolism in over 16s: reducing the risk of hospital-acquired deep vein thrombosis or pulmonary embolism (August 2019)