Systemic Anti Cancer Treatment Protocol

FOLFOX

PROTOCOL REF: MPHAFOLFO
(Version No: 1.2)

This protocol has been temporarily amended - please see the SRG Guidelines during COVID-19 Lower GI cancer

Approved for use in:

Adjuvant colorectal cancer stage 3 or high risk stage 2

Advanced colorectal cancer first line

Advanced colorectal cancer second or third line after irinotecan based therapies

Dosage:

Drug	Dosage	Route	Frequency
Oxaliplatin	85mg/m^2	IV	Every 14 days
Folinic Acid	350mg	IV	Every 14 days
Fluorouracil	400mg/m^2	IV	Every 14 days
Fluorouracil	2400mg/m^2	IV	Every 14 days

Adjuvant – give for 12 cycles

Advanced – give for 6 cycles and review, continue subject to patient choice, tolerability and response

Supportive treatments:

Anti-emetic risk – Moderate

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

Dexamethasone tablets 4mg twice daily for 3 days

Loperamide 2mg after each loose stool

Extravasation risk:

PICC line will be usually inserted. Network guidelines suggest that fluorouracil and oxaliplatin are IRRITANTS and should be treated using Network guidance

Administration:

Day	Drug	Dosage	Route	Diluent and Rate
1	**Dexamethasone** 30 mins before chemotherapy	8mg	PO	
1	**Ondansetron** 30 mins before chemotherapy	16mg	PO	
1	**Oxaliplatin**	85mg/m^2	IV	500mL Glucose 5% infusion over 2 hours
Oxaliplatin and Folinic Acid given at same time concomitantly				
1	**Folinic Acid**	350mg	IV	250mL Glucose 5% infusion over 2 hours
1	**Fluorouracil**	400mg/m^2	IV	Bolus over 5 minutes
1 to 2	**Fluorouracil**	2400mg/m^2	IV	46 hour continuous infusion in Sodium Chloride 0.9%

Notes:

Caution in patients with pre-existing neurotoxicity – see below

Caution in patients with pre-existing heart disease, angina pectoris, arrhythmias

Correct any magnesium deficiency before giving oxaliplatin

Be aware of infusion related allergic reactions – see below

Sorivudine and analogues – Potentially fatal interaction – avoid completely

Main Toxicities:

Oxaliplatin

Infusion reactions, neuro toxicity, myelosuppression, mucositis, diarrhoea, nausea and vomiting

Fluorouracil

Diarrhoea, nausea and vomiting, conjunctivitis / sore eyes, skin rashes, Palmar Plantar Erythema (PPE or hand foot syndrome), stomatitis, chest pain (myocardial ischaemia or angina), ovarian failure / infertility, nail ridges, taste changes

DPD deficiency – leads to severe early fluorouracil toxicity, affects approximately 3% of population, may be life threatening

Investigations and treatment plan

	Pre	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Ongoing
Medical Assessment	X		X		X	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	Every cycle
CrCl	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.
CT scan	X					
Informed Consent	X					
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

Proceed on day 1 if:-

ANC ≥ 1.0 x 10^9/L	Platelets ≥ 75 x 10^9/L

Delay 1 week on day 1 if:-

ANC ≤ 0.9 x 10^9/L	Platelets ≤ 74 x 10^9/L

If WCC, platelets or ANC still below required levels for treatment at week 2, delay treatment again and patient will need assessment and chemotherapy dose reduction as follows.

Lowest count since previous cycle	Oxaliplatin dose	Fluorouracil dose
Grade 3 / 4 neutropenia (<1.0 x10^9/L) or thrombocytopenia (<50 x 10^9/L)	65mg/m^2 (metastatic) 75mg/m^2 (adjuvant)	80% bolus and infusion

Non-haematological toxicity

Renal

Calculate CrCl using Cockroft and Gault before each cycle.

Creatinine Clearance (mL/min)	Oxaliplatin Dose	Fluorouracil dose
≥ 30	Full dose	Full dose
< 30	Omit	75%

If moderate impairment monitor closely and adjust oxaliplatin dose if deterioration or toxicity appears

Hepatic

Liver function	Oxaliplatin dose	Fluorouracil dose
Bilirubin > 3 x ULN	50%	50%

Note that significantly impaired hepatic function might be a sign of disease progression and require cessation or change of treatment.
Always discuss deteriorating organ function with consultant

Oxaliplatin

<table>
<tr><td>Neurotoxicity – see notes below for specific cases</td><td>
<table>
<tr><th>Neurotoxicity</th><th>Oxaliplatin dose</th></tr>
<tr><td>Grade 1 any duration or grade 2 < 7days but resolving before next cycle</td><td>85mg/m^2</td></tr>
<tr><td>Grade 2 persisting for 7 days or Grade 3 resolved by next cycle</td><td>65mg/m^2</td></tr>
<tr><td>Grade 3 persisting to next cycle or any grade 4</td><td>Stop oxaliplatin</td></tr>
</table>
If oxaliplatin is discontinued, review the infusional dose of fluorouracil and consider increasing to 2800mg/m^2
</td></tr>
<tr><td>Acute cold related dysaesthesia (CRD)</td><td>Transient paraesthesia of hands and feet as well as laryngopharyngeal dysaesthesia (unpleasant sensations in throat) is common. Onset is during or within hours of infusion and it resolves in minutes or days. Symptoms are exacerbated by cold – advise patients on suitable precautions e.g. avoid cold drinks. Should not require dose reduction, but if troublesome then infusion duration can be increased to 6 hours (see note below)</td></tr>
<tr><td>Laryngopharyngeal dysaesthesia</td><td>Stop infusion, provide symptomatic treatment. Resume at slower infusion rate. Give subsequent infusions over 6 hours (see note below)</td></tr>
<tr><td>Cumulative dose related sensory neuropathy</td><td>Usually occurs after a cumulative dose of 800mg/m^2. It can occur after treatment is completed, is usually reversible taking about 3-5 months to recover</td></tr>
<tr><td>Allergic reactions during infusion</td><td>Stop the infusion and call for help. Follow trust hypersensitivity policy. Treat with IV corticosteroid and antihistamine. Discuss continuing with fluorouracil alone or re-challenge with the consultant.</td></tr>
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Whilst the recommended increase in duration of infusion is to 6 hours – where the oncologist and the treating team agree, this can be reduced to 4 hours dependent on the severity of the reaction and the tolerability of the infusion over this time.

Fluorouracil

Chest pain, coronary artery spasm	Stop fluorouracil, standard angina investigations, refer to consultant, if symptoms persist stop permanently
Stomatitis	If mouth ulcers or > grade 2 symptoms develop treat symptomatically, delay treatment until resolved to grade 1 and reduce fluorouracil doses by 20%.

	See table
Diarrhoea	Treat diarrhoea between cycles symptomatically. If diarrhoea has not resolved by next cycle delay treatment by 1 week. If diarrhoea remains troublesome or more than 1 delay is required reduce both fluorouracil bolus and infusion doses by 20% and continue at the lower dose unless further toxicity occurs - See table
PPE	Treat symptomatically, delay treatment until resolved to grade 1. Reduce fluorouracil doses (bolus and infusion) by 20% for subsequent doses if persistent troublesome PPE. See table

Fluorouracil dose reductions for non haematological toxicity

	Non haematological toxicity (diarrhoea, stomatitis, PPE)			
Grade	0-1	2	3	4
1st occurrence	100%	80%	50%	Stop treatment
2nd occurrence	80%	70%	50%	Stop treatment
3rd occurrence	50%	50%	50%	Stop treatment

References:

Cheshire and Merseyside Strategic Clinical Networks. Network Guidance for the prevention and management of extravasation injuries V6.0 accessed 11.49 on 26/01/2017 on https://extranet.clatterbridgecc.nhs.uk/index.php/intranet/policies-and-corporate-documents/policies/clinical

Summary of Product Characteristics, Electronic Medicines Compendium, Oxaliplatin accessed 26/01/2017 at 11.58 http://www.medicines.org.uk/emc/medicine/27556 and Fluorouracil 50mg/ml accessed on 26/01/2017 at 12.02 at http://www.medicines.org.uk/emc/medicine/636

NICE technology appraisal No 100, Capecitabine and oxaliplatin in the adjuvant treatment of stage III (Duke's C) colon cancer; Issue April 2006