Systemic Anti Cancer Treatment Protocol

FOLFIRI

PROTOCOL REF: MPHAFOLFI
(Version No: 1.1)

Approved for use in:

Advanced colorectal cancer first line

Advanced colorectal cancer second line

Second line treatment of locally advanced and metastatic gastric / gastro-oesophageal junction adenocarcinoma

Dosage:

Drug	Dosage	Route	Frequency
Irinotecan	180mg/m^2	IV	Every 14 days
Folinic Acid	350mg flat dose	IV	Every 14 days
Fluorouracil	400mg/m^2	IV bolus	Every 14 days
Fluorouracil	2400mg/m^2	IV infusion	Every 14 days

Review after 6 cycles (12 weeks) and continue to 24 weeks if stable disease and acceptable toxicity

Supportive treatments:

Antiemetic risk - moderate

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

Dexamethasone tablets 4mg twice daily for 3 days

Loperamide 4mg immediately after first liquid stool followed by 2mg every 2 hours for at least 12 hours

Extravasation risk:

Fluorouracil and Irinotecan: Irritant - Follow trust/network extravasation policy.

Administration:

Day	Drug	Dosage	Route	Diluent and Rate
1	**Dexamethasone** 30mins prior to chemotherapy	8mg	PO	
1	**Ondansetron** 30mins prior to chemotherapy	16mg	PO	
1	**Atropine**	600 micrograms	SC	Always prior to irinotecan
1	**Irinotecan**	180 mg/m^2	IV	250mL Glucose 5% infusion over 30 to 90 minutes
1	**Folinic Acid**	350mg	IV	250mL Glucose 5% infusion over 2 hours
1	**Fluorouracil**	400mg/m^2	IV	Bolus injection over 5 minutes
1 to 2	**Fluorouracil**	2400mg/m^2	IV	46 hour continuous infusion in Sodium Chloride 0.9%

Cycle 1 irinotecan should be administered over 90 minutes, if tolerated this can be reduced to 60 mins at cycle 2 and 30 mins from cycle 3 onwards.

Administer folinic acid before fluorouracil

Contra – indicated - chronic inflammatory bowel disease and/or bowel obstruction

<u>Drug Interactions</u>

Care with patients on coumarin anticoagulants – monitor INR closely, consider LMWH

St John's Wort – causes accelerated metabolism of irinotecan, reducing potential efficacy - avoid

Atazanavir –increased risk of toxicity of irinotecan as metabolism of irinotecan inhibited

Itraconazole – Increased risk of toxicity - avoid

Ketoconazole - Increased risk of toxicity - avoid

Lapatanib – Rarely used together seek advice from pharmacy

Main Toxicities:

Irinotecan

Myelosuppression, diarrhoea, alopecia, cholinergic syndrome during administration, ovarian failure/infertility

Cholinergic syndrome: Diarrhoea, sweating, blurred vision, dizziness within first 24 hours after irinotecan.

Diarrhoea: This may occur within 30-90 minutes of the infusion or may be delayed. Ensure patients are dispensed loperamide and that they know how and when to take them.

Neutropenia with diarrhoea is a life threatening complication and requires immediate admission and management.

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 all apply:-

ANC ≥ 1.0 x 10^9/L	Platelets ≥ 100 x 10^9/L

Delay 1 week on day 1 if any apply:-

ANC ≤ 0.9 x 10^9/L	Platelets ≤ 99 x 10^9/L

If platelets or ANC still below required levels for treatment at week 2, delay treatment again and reduce fluorouracil and irinotecan doses by 20% for subsequent cycles. If a further delay for myelotoxicity occurs despite a 20% reduction a further 20% reduction may be considered.

Non-haematological toxicity

Renal

Calculate CrCl using Cockroft and Gault formula at baseline and repeat if serum creatinine increases between cycles.

Creatinine Clearance (mL/min)	**Irinotecan Dose**	**Fluorouracil Dose**
≥ 30	Full dose	Full dose
< 30	Use with caution – no data	Give 75%

Hepatic

Liver function	**Irinotecan dose**	**Fluorouracil dose**
Bilirubin between 1.5 to 3 x ULN ALP>5 x ULN	50%	100%
Bilirubin > 3 x ULN	Omit	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**

Irinotecan

Diarrhoea	This may be due to irinotecan and / or fluorouracil. Always treat as irinotecan induced
Diarrhoea within first 24 hours	This is likely to be caused by an acute cholinergic syndrome, do not take loperamide within the first 24 hours. Advise patient to contact chemotherapy team – and consider repeat dose of atropine.
Delayed diarrhoea (after 24 hours post irinotecan)	Once a liquid stool occurs loperamide 4mg should be taken immediately, followed by 2mg every 2 hours for at least 12 hours, and for 12 hours following the last liquid stool. Patients should be instructed to drink large volumes of water or electrolytes. Do not continue high dose loperamide for longer than 48 hours Any concomitant fever or vomiting will require hospitalisaton for rehydration If diarrhoea persists for 24 hours despite loperamide, consider ciprofloxacin 250mg BD if neutropenic (ANC ≥ 1.0 x 10^9/L) orally for 7 days If diarrhoea persists after 48 hours then patients should be hospitalised for further management and treatment review. Do **not** use loperamide prophylactically even if delayed diarrhoea occurred in previous cycles. For first episode of diarrhoea grade 1 or higher, delay treatment for 1 to 2 weeks until completely resolved and reduce dose of irinotecan in subsequent cycles by 25%. Reduce fluorouracil dose as well – see below

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 toxicities (diarrhea, 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:

Cunningham, D et al, Lancet 1998; Vol 352: 1413 – 1418

Rougier et al, Lancet 1998; Vol 352; 1407 – 1412

Summary of Product Characteristics,Electronic Medicines Compendium, Irinotecan, https://www.medicines.org.uk/emc/medicine/27592

FOCUS trial (CRO8); MRC Colorectal cancer group, (Protocol Version 6) January 2003