Systemic Anti Cancer Treatment Protocol

Cetuximab & FOLFIRI

PROTOCOL REF: MPHACETFOFI
(Version No: 1.1)

Approved for use in:

Cetuximab (NICE TA439) is recommended, within its marketing authorisation, as an option for previously untreated epidermal growth factor receptor (EGFR)-expressing, RAS wild-type metastatic colorectal cancer in adults in combination with:

- 5-fluorouracil, folinic acid and oxaliplatin (FOLFOX) or
- 5-fluorouracil, folinic acid and irinotecan (FOLFIRI).

This guidance replaces TA176.

In some instances patients may receive ox-cap or I-cap in place of their FOLFOX or FOLFIRI when patients do not wish to have a line fitted.

Dosage:

Drug	Dosage	Route	Frequency
Cetuximab	500mg/m^2	IV	Every 14 days
Irinotecan	180mg/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

Advanced – give for 6 cycles and review.

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

Pliazon® cream

Extravasation risk:

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

Administration:

Day	Drug	Dosage	Route	Diluent and Rate
1	**Dexamethasone** 30 min prior to chemotherapy	8mg	PO	
1	**Ondansetron** 30 min prior to chemotherapy	16mg	PO	
1	**Chlorphenamine**	10mg	IV	Bolus
1	**Cetuximab**	500mg/m^2	IV	Infuse first dose over 2 hours then reduce to 90 -60 minutes as tolerated
	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 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

Drug Interactions

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

Notes:
Administer cetuximab before chemotherapy
Caution in patients with pre-existing neurotoxicity – see below
Caution in patients with pre-existing heart disease, angina pectoris, arrhythmias
Be aware of infusion related allergic reactions – see below
Sorivudine and analogues – Potentially fatal interaction – avoid completely

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

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

Main Toxicities:

Cetuximab

Skin reactions, cholinergic syndrome, Infusion related reactions, electrolyte disturbances, neutropenia, cardiovascular, conjunctivitis / keratitis

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 WCC, platelets or ANC still below required levels for treatment at week 2, delay treatment again and reduce flourouracil 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. Refer to oncologist.

Note that cetuximab is not myelosuppressive and no dose reduction is required.

Non-haematological toxicity

<table>
<tr><td>Renal</td><td>Calculate CrCl using Cockroft and Gault formula at baseline and repeat if serum creatinine increases between cycles.
<table>
<tr><th>Creatinine Clearance (mL/min)</th><th>Irinotecan Dose</th><th>Fluorouracil Dose</th></tr>
<tr><td>≥ 30</td><td>Full dose</td><td>Full dose</td></tr>
<tr><td>< 30</td><td>Use with caution – no data</td><td>Give 75%</td></tr>
</table>
No dose adjustment required with cetuximab</td></tr>
<tr><td>Hepatic</td><td>
<table>
<tr><th>Liver function</th><th>Irinotecan dose</th><th>Fluorouracil dose</th></tr>
<tr><td>Bilirubin between 1.5 to 3 x ULN ALP>5 x ULN</td><td>50%</td><td>100%</td></tr>
<tr><td>Bilirubin > 3 x ULN</td><td>Omit</td><td>50%</td></tr>
</table>
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</td></tr>
</table>

<table>
<tr><th colspan="2">Cetuximab</th></tr>
<tr><td>Dermatological</td><td>Skin reactions are very common and treatment interruption or discontinuation may be required. Prophylactic use of oral tetracyclines (6 - 8 weeks) and topical application of 1% hydrocortisone cream with moisturiser should be considered.

If a patient experiences an intolerable or severe skin reaction (≥ grade 3) cetuximab therapy must be interrupted. Treatment may only be resumed if the reaction has resolved to grade 2.

Recommended dose modifications for management of severe skin reactions:

<table>
<tr><td>≥ grade 3 skin reaction</td><td>Cetuximab dose after resolution to ≤ grade 2</td></tr>
<tr><td>1st occurrence</td><td>Resume at full dose</td></tr>
<tr><td>2nd occurrence</td><td>400mg/m^2</td></tr>
<tr><td>3rd occurrence</td><td>300mg/m^2</td></tr>
<tr><td>4th occurrence</td><td>Discontinue treatment</td></tr>
</table>
</td></tr>
<tr><td>Ocular</td><td>Patients presenting with signs and symptoms suggestive of keratitis such as acute or worsening: eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye should be referred promptly to an ophthalmology specialist.

If a diagnosis of ulcerative keratitis is confirmed, treatment with cetuximab should be interrupted or discontinued. If keratitis is diagnosed, the benefits and risks of continuing treatment should be carefully considered.</td></tr>
<tr><td>Hypersensitivity reactions including anaphylaxis</td><td>Mild or moderate infusion-related reactions are very common: comprising symptoms such as fever, chills, dizziness or dyspnoea that predominately occur when patients receive their first cetuximab infusion.

If the patient experiences a mild or moderate infusion-related reaction, the infusion rate may be decreased. It is recommended to maintain this lower infusion rate in all subsequent infusions.

Close monitoring of patients, particularly during the first administration, is required. Special attention is recommended for patients with reduced performance status and pre-existing cardio-pulmonary disease.</td></tr>
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<table>
<tr><td></td><td>If an infusion-related reaction develops later during the infusion or at a subsequent infusion further management will depend on its severity:

<table>
<tr><td>Infusion related reaction (NCI CTC version 4)</td><td>Management</td></tr>
<tr><td>Grade 1</td><td>Slow the rate of infusion to a previously tolerated rate, decrease the infusion rate by 50% and the patient keep under close supervision.</td></tr>
<tr><td>Grade 2</td><td>Decease the infusion rate by 50% and immediately administer treatment for symptoms, and the patient keep under close supervision.</td></tr>
<tr><td>Grade 3 and 4</td><td>Stop infusion immediately, treat symptoms. The patient should receive no further treatment with cetuximab</td></tr>
</table>

A cytokine release syndrome (CRS) typically occurs within one hour on the infusion and is less commonly associated with bronchospasm and urticaria. CRS is normally most severe in relation to the first infusion.</td></tr>
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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

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. Contact chemotherapy team
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 diarrhea 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 dose reductions for non haematological toxicity

	Non haematological toxicities (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:

Summary of product characteristics, Electronic Medicines Compendium, Erbitux,

https://www.medicines.org.uk/emc/medicine/19595

Management of skin rash during egfr-targeted monoclonal antibody treatment for gastrointestinal malignancies: Canadian recommendations; Curr Oncol. 2009 Jan; 16(1): 16–26. http://www.ncbi.nlm.nih.gov

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

Cetuximab and panitumumab for previously untreated metastatic colorectal cancer, NICE Guidance accessed on 05/07/2017 on https://www.nice.org.uk/guidance/ta439