Systemic Anti Cancer Treatment Protocol

Cetuximab & FOLFOX

PROTOCOL REF: MPHACETFOL
(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:

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
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

To be given for 6 cycles then review, continue until disease progression or unacceptable toxicity.

Supportive treatments:

Anti Emetic Risk - Moderate

Pliazon® cream

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

Fluorouracil – Irritant, follow trust/network extravasation policy.

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	**Chlorphenamine** Prior to cetuximab	10mg	IV	Bolus injection
1	**Cetuximab**	500mg/m^2	IV	Infuse first dose over 2 hours then reduce to 1 hour as tolerated
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:

Be aware of possible infusion related reactions with cetuximab and oxaliplatin and administer pre-meds as prescribed

Administer cetuximab before chemotherapy

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:

Cetuximab

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

Oxaliplatin

Infusion reactions, neurotoxicity, 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 all apply:-

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

Delay 1 week on day 1 if any apply:-

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

If 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

Note that cetuximab is not myelosuppressive and no dose reduction is needed.
If further dose reduction is required refer to oncologist. Do not increase the dose of fluorouracil once reduced.

Non-haematological toxicity

Renal

Calculate CrCl using Cockroft and Gault before each cycle. If renal function falls by >30% than expected value consider EDTA clearance

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

Hepatic

Liver function	**Oxaliplatin dose**	**Fluorouracil dose**
Bilirubin > 3 x ULN	100%	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**

<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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If an infusion-related reaction develops later during the infusion or at a subsequent infusion further management will depend on its severity:

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

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.

Oxaliplatin

Neurotoxicity – see notes below for specific cases

Neurotoxicity	Oxaliplatin dose
Grade 1 any duration or grade 2 < 7days but resolving before next cycle	85mg/m^2
Grade 2 persisting for 7 days or Grade 3 resolved by next cycle	65mg/m^2
Grade 3 persisting to next cycle or any grade 4	Stop oxaliplatin

If oxaliplatin is discontinued, review the infusional dose of fluorouracil and consider increasing to 2800mg/m^2

Acute cold related dysaesthesia (CRD)

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)

Laryngopharyngeal dysaesthesia	Stop infusion, provide symptomatic treatment. Resume at slower infusion rate. Give subsequent infusions over 6 hours (see note below)
Cumulative dose related sensory neuropathy	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
Allergic reactions during infusion	Stop the infusion and call for help. Follow trust anaphylaxis policy. Treat with IV corticosteroid and antihistamine. Discuss continuing with fluorouracil alone or re-challenge with the consultant.

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
Chest pain, coronary artery spasm	Stop fluorouracil, standard angina investigations, refer to consultant, if symptoms persist stop permanently

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/pmc/articles/PMC2644628/

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

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