Systemic Anti-Cancer Treatment Protocol

Cetuximab, Carboplatin and Fluorouracil Head and Neck Cancer

PROCTOCOL REF: MPHACECAFL
(Version No: 1.2)

Approved for use in:

Head and neck cancer locally advanced/metastatic disease – 1st line treatment

Dosage:

Drug	Dose	Route	Frequency
Cetuximab	**Loading dose cycle 1 day 1 one only 400mg/m^2** **Maintenance dose cycle 2 onwards 250mg/m^2**	IV	Day 1 of a 21 day cycle
Cetuximab	**250mg/m^2**	IV	Day 8 and day 15 of a 21 day cycle
Carboplatin	**Dose (mg) = target AUC5 (mg/ml x min) x [GFR ml/min + 25]**	IV	Day 1 of a 21 day cycle
Fluorouracil	**1000mg/m^2/day over 24 hours**	IV	Day 1 to 4 of a 21 day cycle

Repeat at 21 day intervals for 6 cycles of combination then continue with cetuximab as single agent

Supportive Treatments:

Domperidone 10mg three times a day

Dexamethasone 4mg twice a day for 3 days on days 2 to 4

Pliazon cream apply topically when required two to four times a day

Extravasation risk:

Refer to local guidelines

Administration:

Cetuximab is administered undiluted and has a maximum infusion rate of 10mg/minute. The first infusion should be administered over 2 hours, and if tolerated this can be reduced at subsequent infusions

Inpatient regimen

Day	Drug	Dose	Route	Diluent and rate
1	**Dexamethasone**	**8mg**	**IV**	30mins before chemotherapy
	Chlorphenamine	**10mg**	**IV**	30mins before chemotherapy
	Ondansetron	**16mg**	**IV**	30mins before chemotherapy
	Cetuximab	**Loading dose cycle 1 only 400mg/m^2**	**IV**	Over 120 minutes
		Maintenance dose cycle 2 onwards 250mg/m^2	**IV**	Over 60 minutes
	Carboplatin	**AUC5**	**IV**	Glucose 5% 500mL over 60 minutes
	Fluorouracil	**1000mg/m^2**	**IV**	Sodium Chloride 0.9% 1000mL over 24 hours
2	**Fluorouracil**	**1000mg/m^2**	**IV**	Sodium Chloride 0.9% 1000mL over 24 hours
3	**Fluorouracil**	**1000mg/m^2**	**IV**	Sodium Chloride 0.9% 1000mL over 24 hours
4	**Fluorouracil**	**1000mg/m^2**	**IV**	Sodium Chloride 0.9% 1000mL over 24 hours
8	**Dexamethasone**	**8mg**	**IV**	30mins before chemotherapy
	Chlorphenamine	**10mg**	**IV**	30mins before chemotherapy
	Cetuximab	**250mg/m^2**	**IV**	Over 60 minutes
15	**Dexamethasone**	**8mg**	**IV**	30mins before chemotherapy
	Chlorphenamine	**10mg**	**IV**	30mins before chemotherapy

	Cetuximab	**250mg/m^2**	**IV**	Over 60 minutes

Outpatient regimen

Day	Drug	Dose	Route	Diluent and rate
1	**Dexamethasone**	**8mg**	**IV**	30mins before chemotherapy
	Chlorphenamine	**10mg**	**IV**	30mins before chemotherapy
	Ondansetron	**16mg**	**IV**	30mins before chemotherapy
	Cetuximab	**Loading dose cycle one only 400mg/m^2**	**IV**	Over 120 minutes
		Maintenance dose cycle 2 onwards 250mg/m^2		Over 60 minutes
	Carboplatin	**AUC5**	**IV**	Glucose 5% 500ml over 60 minutes
	Fluorouracil	**4000mg/m^2**	**IV**	Sodium Chloride 0.9% via LV 2 infusor pump over 96 hours. Total volume 195mls
8	**Dexamethasone**	**8mg**	**IV**	30mins before chemotherapy
	Chlorphenamine	**10mg**	**IV**	30mins before chemotherapy
	Cetuximab	**250mg/m^2**	**IV**	Over 60 minutes
15	**Dexamethasone**	**8mg**	**IV**	30mins before chemotherapy
	Chlorphenamine	**10mg**	**IV**	30mins before chemotherapy
	Cetuximab	**250mg/m^2**	**IV**	Over 60 minutes

Main Toxicities:

Haematological: Myelosuppression: neutropenia, thrombocytopenia and anaemia

Gastrointestinal: Anorexia, nausea, vomiting and diarrhoea, mucositis

Alopecia, fatigue, loss of fertility

Cetuximab	
Dermatological	Main adverse reactions of cetuximab are skin reactions which may become severe; mainly present as acne-like rash and/or, less frequently, as pruritus, dry skin, desquamation, or nail disorders The majority of skin reactions develop within the first three weeks of therapy. Cetuximab causes sun-sensitivity that may exacerbate skin reactions. Patients should be counselled to protect themselves from sunlight.
Hepatobiliary	Increase in liver enzymes (AST, ALT, ALP)
Ocular	Keratitis - acute or worsening: eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye should be referred promptly to an ophthalmology specialist
Additional side effects	**Hypersensitivity reactions** including anaphylaxis (infusion-related reactions occur with mild to moderate symptoms in more than 10% of patients)
	Hypomagnesaemia, hypocalcaemia
Carboplatin	
Nephrotoxicity	Impairment of renal function is more likely in patients who have previously experienced nephrotoxicity as a result of cisplatin therapy
Neuropathies	Peripheral neuropathy – more common in elderly patients and those previously treated with cisplatin.
Hepatobiliary toxicity	Raised liver function tests
Ocular	Rare reports of transient visual disturbances, which may include transient sight loss

Ototoxicity	Decreases in hearing acuity, consisting of high-frequency hearing loss In patients who have been previously treated with cisplatin and have developed hearing loss related to treatment, the hearing impairment may persist or worsen.
Additional side effects	Anaphylactic-like reactions to carboplatin have been reported Pulmonary fibrosis manifested by tightness of the chest and dyspnoea.

Fluorouracil	
Ocular	Nystagmus, watery eyes from increased production of tears, gritty, red, sore eyes and blurred vision
Hepatobiliary	Liver cell damage, liver necrosis, biliary sclerosis, cholecystitis
Dermatological	Palmar – plantar syndrome (hand-foot syndrome), on the palms of the hands and soles of the feet Hyperpigmentation of the skin Brittle, chipped and ridged nails –blue tinge or darkening or the nails, flaking of the nails, or pain and thickening of the nail bed.
Cardiovascular	Common - Angina, Ischemic ECG abnormalities Uncommon - Arrhythmia, myocardial infarction, myocardial ischaemia myocarditis, dilative cardiomyopathy, cardiac shock. **Vascular disorders** Cerebral, intestinal and peripheral ischemia

Investigations:

	Pre	Cycle 1	C1 d8	C1 d15	Cycle 2	Cycle 3	Ongoing
Medical Assessment	X					X	After Cycle 6. Then every 3 months and at end of treatment
Nursing Assessment		X	X	X	X	X	Every cycle
FBC	X				X	X	Every cycle, day 1 only
U&E & LFT	X		X	X	X	X	Every cycle, day 1 only
Calculate CrCl	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						As clinically indicated
Informed Consent	X						
PS recorded	X	X	X	X	X	X	Every visit
Toxicities documented	X	X	X	X	X	X	Every visit
Weight recorded	X	X	X	X	X	X	Every visit

FBC and biochemistry should be monitored on day 8 and day 15 of cycle 1. For subsequent cycles FBC and biochemistry are only required on day 1 of cycle unless there are specific symptoms that suggest repeating, for example vomiting or diarrhoea that increase the risk of dehydration

Dose Modifications and Toxicity Management:

<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>200mg/m^2</td></tr>
<tr><td>3rd occurrence</td><td>150mg/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.</td></tr>
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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.

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.

Carboplatin	**Recommended dose reduction for toxicity**
First dose reduction	AUC4
Second dose reduction	AUC3

Fluorouracil	**Recommended dose reduction for toxicity =**
First dose reduction	750mg/m^2
Second dose reduction	500mg/m^2

Haematological Toxicity:

Proceed on day 1 if-

ANC ≥ 1.0 x 10^9/L	Plt ≥ 100 x 10^9/L

Delay 1 week and consider dose reduction on day 1 if-

ANC ≤ 0.9 x 10^9/L	Plt ≤ 99 x 10^9/L

Hepatic impairment:

Fluorouracil		
Bilirubin /µmol/L	**AST/ALT /units**	**Dose**
<85	<180	No dose modification
>85	or >180	Contra indicated
Although 50 to 80% of fluorouracil is metabolised by the hepatic route, the clinical significance is unclear. Some studies of plasma and tissue concentration of the drug and derivatives in patients with hepatocellular carcinoma and liver cirrhosis or liver metastases detected no change in drug disposition relating to liver dysfunction, indicating no dose reduction is required. A dose reduction of the initial dose is advised of 1/3 to ½ in hepatic impairment, is recommended, which may be increase on subsequent cycles if no toxicity is observed.		

Renal impairment:

Carboplatin
Excretion is primarily by glomerular filtration in urine, with most of the drug excreted in the first 6hrs. ~32% dose is excreted unchanged. Patients with creatinine clearance values of less than 60 mL/min are at greater risk to develop myelosuppression. In case of a glomerular filtration rate of ≤ 20 mL/min, carboplatin should not be administered.

Fluorouracil
Fluorouracil is predominantly eliminated by the liver. Following a single IV dose, ~15% dose is excreted unchanged in the urine. Consider dose reduction in severe renal impairment only in patients with creatinine clearance below 30m/min.

References:

Carboplatin 10mg/ml concentrate for solution for infusion, summary of Product Characteristics, Accord Healthcare limited, Middlesex. 09/12/2008. Available from www.medicines.org.uk/emc/medicine. Last updated 26/02/14.

Erbitux 5mg/ml solution for infusion, Summary of Product Characteristics. Merck Serono, Middlesex 29/06/2004. Available from www.medicines.org.uk/emc/medicine. Last updated 04/08/2014.

Fluorouracil 50 mg/ml Solution for Injection or Infusion, Summary of Product Characteristics, Hospira, Warwickshire. 19/07/2004. Available from https://www.medicines.org.uk/emc Last updated 24/07/14.

Dosage Adjustment for Cytotoxics in Hepatic Impairment. January 2009 UCLH (Version 3 - updated January 2009)

Dosage Adjustment for Cytotoxics in Renal Impairment. January 2009 UCLH (Version 3 - updated January 2009)