Systemic Anti-Cancer Treatment Protocol

Cetuximab, Cisplatin and Fluorouracil Head and Neck Cancer

PROTOCOL REF: MPHACECIFL
(Version No: 2.0)

Approved for use in:

NICE TA guidance 473 (31st August 2017) –

Recurrent or metastatic squamous carcinoma of the head and neck originating in the oral cavity only.

All patients must be registered on Blueteq system before treatment initiated.

Creatinine clearance at baseline > 50mL/min

(Note: existing patients previously registered with CDF for cetuximab for head and neck cancers not originating from the oral cavity can remain on treatment until it is considered appropriate to stop)

Dosage:

Drug	Dose	Route	Frequency
Cetuximab	**Loading dose cycle 1 day 1 only 400mg/m^2**	IV	Day 1 of a 21 day cycle
	Maintenance dose cycle 2 onwards 250mg/m^2		
Cetuximab	**250mg/m^2**	IV	Day 8 and day 15 of a 21 day cycle during chemotherapy
Cisplatin	**80mg/m^2**	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

On completion of chemotherapy patients should switch to cetuximab every 2 weeks:

Drug	Dose	Route	Frequency
Cetuximab	**500mg/m^2**	IV	Every 2 weeks

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:

Cisplatin: Injection site reactions may occur during the administration of cisplatin. Given the possibility of extravasation, it is recommended to closely monitor the infusion site for

possible infiltration during drug administration. A specific treatment for extravasation reactions is unknown at this time

Fluorouracil: refer to local guidelines for management extravasation

Cetuximab: refer to local guidelines

Administration:

- Review patient's fluid intake over the previous 24 hours
- Review common toxicity criteria and performance status
- Calculate creatinine clearance using Cockcroft and Gault equation (see investigation section)
- Weigh the patient prior to commencing intravenous fluids
- Commence strict fluid balance (input and output)

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

Cockcroft and Gault formula

Male patients $\frac{1.23 \times (140 - \text{age}) \times \text{weight (kg)}}{\text{Serum Creatinine (micromol/L)}}$

Female patients $\frac{1.04 \times (140 - \text{age}) \times \text{weight (kg)}}{\text{Serum Creatinine (micromol/L)}}$

Inpatient regimen

Day	Drug	Dose	Route	Diluent and rate
1	**Fosaprepitant** 30mins before chemotherapy	**150mg**	**IV**	Sodium Chloride 0.9% 100mL over 20 to 30 minutes
	Chlorphenamine 30 minutes before chemotherapy	**10mg**	**IV**	Bolus injection
	Ondansetron 30mins before chemotherapy	**16mg**	**IV**	Bolus injection
	Dexamethasone 30mins before chemotherapy	**8mg**	**IV**	Bolus injection
	Furosemide tablets	**20mg**	**PO**	
	Cetuximab	**Loading dose cycle one only 400mg/m^2**	**IV**	Over 120 minutes
		Maintenance dose cycle 2 onwards 250mg/m^2	**IV**	Over 60 minutes
	Sodium Chloride 0.9% 1000mL With 20mmol Potassium Chloride		**IV over 90 minutes**	
	Measure urine output volume and record **If urine output averages 100mL/hour over previous 3 hours then proceed with cisplatin infusion** **If urine output is less than 100mL/hour the patient should be assessed and further 500mL sodium chloride 0.9% given IV over 30 minutes** **If urine output still not adequate contact the head and neck team**			
	Cisplatin	**80mg/m^2**	**IV**	Sodium Chloride 0.9% 1000mL over 90 minuets
	Sodium Chloride 0.9% 1000mL With 20mmol Potassium Chloride		IV over 90 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	**Chlorphenamine** 30mins before cetuximab	**10mg**	**IV**	Bolus injection
	Dexamethasone 30mins before cetuximab	**8mg**	**IV**	Bolus injection
	Cetuximab	**250mg/m^2**	**IV**	Over 60 minutes
15	**Chlorphenamine** 30mins before cetuximab	**10mg**	**IV**	Bolus injection
	Dexamethasone 30mins before cetuximab	**8mg**	**IV**	Bolus injection
	Cetuximab	**250mg/m^2**	**IV**	Over 60 minutes

Outpatient regimen

Day	Drug	Dose	Route	Diluent and rate
1	**Fosaprepitant** 30mins before chemotherapy	**150mg**	**IV**	Sodium Chloride 0.9% 100mL over 20 to 30 minutes
	Ondansetron 30mins before chemotherapy	**16mg**	**IV**	Bolus injection
	Chlorphenamine 30 minutes before chemotherapy	**10mg**	**IV**	Bolus injection
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	Furosemide tablets	**20mg**	**PO**	
	Cetuximab	**Loading dose cycle one only 400mg/m^2**	**IV**	Over 120 minutes
		Maintenance dose cycle 2 onwards 250mg/m^2	**IV**	Over 60 minutes

	Sodium Chloride 0.9% 1000mL With 20mmol Potassium Chloride		IV over 90 minutes	
	Measure urine output volume and record **If urine output averages 100mL/hour over previous 3 hours then proceed with cisplatin infusion** **If urine output is less than 100mL/hour the patient should be assessed and further 500mL sodium chloride 0.9% given IV over 30 minutes** **If urine output still not adequate contact the head and neck team**			
	Cisplatin	**80mg/m^2**	**IV**	Sodium Chloride 0.9% 1000mL over 90 minutes
	Sodium Chloride 0.9% 1000mL With 20mmol Potassium Chloride		IV over 90 minutes	
	Fluorouracil	**4000mg/m^2** **(1000mg/m^2/day for 4 days)**	**IV**	Sodium Chloride 0.9% via LV 2 infusor pump over 96 hours. Total volume 195mls
8	**Chlorphenamine** 30 minutes prior to cetuximab	10mg	**IV**	Bolus injection
8	**Dexamethasone** 30mins before chemotherapy	8mg	**IV**	Bolus injection
8	**Cetuximab**	**250mg/m^2**	**IV**	Over 60 minutes
15	**Chlorphenamine** 30 minutes prior to cetuximab	10mg	**IV**	Bolus injection
15	**Dexamethasone** 30mins before chemotherapy	8mg	**IV**	Bolus injection
15	**Cetuximab**	**250mg/m^2**	**IV**	Over 60 minutes

At the end of IV fluids:

- **Weigh the patient and review fluid balance chart**
- **If there is a positive balance of 1.5L or 1.5kg in weight gained then consider furosemide 20mg orally and review output after 30 minutes. Any concerns then discuss with medical team prior to discharging the patient.**

Ensure good oral (or via PEG) fluid intake

- **Confirm patient understanding of the importance of fluid intake**
- **Patient should ensure they have 2 liters of fluid in the 24 hours following chemotherapy**

Main Toxicities:

Haematological: Myelosuppression: neutropenia, thrombocytopenia, anaemia

Gastrointestinal: Anorexia, nausea, vomiting and diarrhoea, mucositis (stomatitis, oesophagitis, pharyngitis, proctitis), bitter or metallic taste disturbance

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

Cisplatin	
Nephrotoxicity	Urine output of 100 mL/hour or greater will help minimise cisplatin nephrotoxicity
Neuropathies	May be irreversible and may manifest by paresthesia, loss of muscle reflex and a sensation of vibrations. A neurologic examination must be carried out at regular intervals.
Ototoxicity	Observed in up to 31% of patients can be unilateral or bilateral and tends to become more frequent and severe with repeated doses; consider audiometry and referral to ENT specialist
Additional side effects	Anaphylactic-like reactions
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. Sensitivity of the skin to sunlight
Cardiovascular	Common - Angina, Ischemic ECG abnormalities Uncommon - Arrhythmia, myocardial infarction, myocardial ischemia myocarditis, dilative cardiomyopathy, cardiac shock. Very rare - Cardiac arrest, sudden cardiac death **Vascular disorders** Cerebral, intestinal and peripheral ischemia

Investigations and treatment plan:

	Pre	Cycle 1	C1 d8	C1 d15	Cycle 2	Cycle 3	Ongoing
Medical Assessment	X	X			X	X	
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
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:

Cetuximab	
Dermatological	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></td><td>
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<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.

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:
<table>
<tr><td>Infusion related reaction (CTC v4)</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</td></tr>
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		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.

Cisplatin	**Recommended dose reduction for toxicity**
First dose reduction	60mg/m^2
Second dose reduction	40mg/m^2

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:

Cisplatin: No dose reduction necessary.

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. However, a dose reduction of the initial dose is advised of 1/3 to ½ in hepatic impairment, which may be increase if no toxicity is observed.			

Renal impairment:

Cisplatin: GFR (mL/min)	**Dose**
Above 60	80mg/m^2 (100% dose)
45 to 59	60mg/m^2 (75% dose)
Below 45	Consider carboplatin

Fluorouracil
Fluorouracil is predominantly eliminated by liver 60-80% is excreted as respiratory $CO_{2,}$ 2-3% by biliary system. Following a single IV dose; approximately 15% of the dose is excreted unchanged in the urine. Consider dose reduction in severe renal impairment only in patients with creatinine clearance below 30mL/min.

References:

Cisplatin 1 mg/ml Sterile Concentrate, Summary of Product Characteristics Hospira UK Ltd Warwickshire.06/09/1996. Available from www.medicines.org.uk/emc/medicine. Last updated 30/04/2013.

Fluorouracil 50 mg/ml Solution for Injection or Infusion, Summary of Product Characteristics, Hospira, Warwickshire. 19/07/2004. Available from www.medicines.org.uk/emc/medicine. 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)