CETUXIMAB, CISPLATIN & 5-FLUOROURACIL

First-line treatment for recurrent or metastatic SCC of Head & Neck after radical surgery or radiotherapy, only if the cancer started in the oral cavity (i.e. lips, tongue, floor of mouth, palate and mouth)

Blueteq registration is required before treatment with cetuximab may start.

Drugs/Dosage:

Cetuximab	400mg/m^2 loading dose	IV	Day 1 of Cycle 1
then	250mg/m^2	IV	Day 1, Day 8 & Day 15
Cisplatin	80mg/m^2	IV	Day 1*
5 Fluorouracil	1000mg/m^2/24hr	IV	Day 1 – Day 4*

*For Cycle 1 only, due to the long administration times, give cetuximab on Day 1 and give **cisplatin and 5FU on Day 2.**

Then, after 6 cycles of chemotherapy completed;

Cetuximab	500mg/m^2	IV	monotherapy every 2 weeks until progressive disease

Other drugs:

Pre-emptive management for all patients starting cetuximab:

- Pliazon cream applied to face, hands, feet, neck, back and chest twice daily throughout treatment (available free of charge from nurse-led or pharmacy)
- advise to limit skin exposure to sun, and to apply sunscreen SPF 15 or higher before going outdoors in sunny weather.
- Doxycycline 100mg od x 14 capsules should also be prescribed routinely with the first cetuximab dose, labelled to be started only at the first appearance of a rash.

Premedication for cetuximab:

Chlorphenamine	10mg	IV	} administered 30 mins prior to cetuximab
Dexamethasone	8mg	IV	}

(Note that anti-emetic IV dex will not be needed pre-chemotherapy)

Administration:

Cetuximab must be administered before chemotherapy on days when chemotherapy is due.

Weekly cetuximab: loading dose over 120 minutes, then all subsequent doses over 60 minutes

Cetuximab 2-weekly: give the first dose over 120 minutes. If the 1st dose is tolerated, all subsequent doses to be given over 90 minutes

Patients need to be observed for one hour after doses 1 and 2 of cetuximab, to ensure no delayed reaction, and any chemotherapy should not be initiated earlier than 1 hour after the end of the cetuximab infusion. If no delayed reactions are observed with doses 1 and 2 of cetuximab, all further chemotherapy may be administered immediately after cetuximab completed[1].

Cisplatin:

1 litre 0.9% sodium chloride + 20mmol KCl + 10mmol $MgSO_4$ IV over 2 hours
Mannitol 20% 100ml IV over 15 minutes
Cisplatin in 1 litre 0.9% sodium chloride IV over 3 hours
1 litre 0.9% sodium chloride + 20mmol KCl + 10mmol $MgSO_4$ IV over 2 hrs
500ml 0.9% sodium chloride IV **or** 500ml - 1 litre water orally over 1 hour
5FU continuous IV infusion over 4 days, given via CVC and ambulatory infusion device

Reason for Update: NICE approved (for oral cavity only); Regular Investigations reviewed	Approved by Consultant: Dr S Whitaker
Version: 4	Approved by Lead Chemotherapy Nurse: S Wills-Percy
Supersedes: Version 3	Date: 2.11.17
Prepared by: S Taylor	Checked by: C Tucker

Frequency: Cisplatin + 5FU: 3 weekly cycle for 6 cycles
Cetuximab administered weekly (Day 1, Day 8 and Day 15 of each cycle) during chemotherapy, then every 2 weeks as monotherapy until disease progression

Main Toxicities: myelosuppression; neuropathy / ototoxicity; mucositis; diarrhoea
coronary artery spasm (see Comments); nephrotoxicity; palmar-plantar erythema;
alopecia (mild); allergic infusion-related reactions to cetuximab (see Comments);
skin reactions to cetuximab (acne-like rash, dry skin, itching, nail changes);
sore eyes; hypomagnesaemia; ovarian failure/infertility

Anti-emetics: Day 1: highly emetogenic; Cetuximab + 5FU: mildly emetogenic

Extravasation: non-vesicants

Regular Investigations:

Cetuximab + chemotherapy

FBC	Day 1, and Day 8 & 15 *of Cycle 1 only*
U&Es & LFTs	Day 1, and Day 8 & 15 *of Cycle 1 only*
Ca^{2+}	Day 1, and Day 8 & 15 *of Cycle 1 only*
Mg^{2+}	Day 1, and Day 8 & 15 *of Cycle 1 only*
EDTA	prior to 1st cycle

After Cycle 1, FBC, U&Es, LFTs & Mg^{2+} are not routinely required on Day 8 & Day 15, unless there are specific symptoms that suggest repeating, e.g. vomiting or diarrhoea.

Cetuximab maintenance
When cetuximab is given as a single agent until progression, the blood tests above are recommended to be assessed 4 weekly i.e. only before every **alternate** dose

Comments: If the patient has any baseline hearing problems, carboplatin AUC 5 should be substituted for cisplatin, administered as discussed below under Renal Impairment.

Allergic reactions to cetuximab: If the patient experiences a mild or moderate infusion-related reaction, the infusion may be re-initiated at a reduced rate. It is recommended to maintain this lower infusion rate in all subsequent infusions.
A severe allergic reaction requires immediate and permanent discontinuation of cetuximab. Infusion-related and pulmonary symptoms may also rarely occur several hours after the cetuximab infusion is given. Patients should be warned about this and instructed to contact the hospital if any such symptoms occur.

If there is a gap of ≥ 4 weeks between weekly doses of cetuximab, the patient must be given another loading dose of 400mg/m^2 cetuximab over 2 hours. (No loading dose required with 2-weekly cetuximab)

For patients on Cycle 1 whose EDTA is not yet available, Cockcroft & Gault may be used to predict GFR. Cisplatin dose should be adjusted if necessary once EDTA available. EDTA should only be repeated if the result is borderline at the start of treatment or if there is a 30% change in serum creatinine.

Weight should be recorded prior to and at the end of cisplatin treatment, and a strict fluid balance chart should be maintained. An average urine output of at least 100ml/hr must be maintained throughout treatment, and cisplatin infusion should not be commenced unless this urine output is achieved. If the urine output is inadequate, the patient should be assessed and urine output increased by administering 500ml sodium chloride 0.9% IV +/- furosemide 20 –

40mg. Furosemide 20 – 40mg po may also be given if there is a positive fluid balance of 1.5 litres, a weight gain of 1.5kg or symptoms of fluid overload. The patient should be asked to drink 2 litres of fluid in the 24hrs following treatment, and to contact the hospital if this is impossible because of problems e.g. nausea and vomiting.

Check electrolytes – additional supplementation of magnesium, calcium or potassium may be required.

Coronary artery spasm is a recognised complication of 5FU although the evidence base regarding aetiology, management and prognosis is not particularly strong. Coronary artery spasm is more common in patients receiving continuous infusions of 5FU, and is usually reversible on discontinuing the infusion. Should a patient receiving 5FU present with chest pains, stop the 5FU. Standard investigation and treatment of angina may be required. If re-challenge is deemed necessary, this can be performed under close supervision, but should symptoms redevelop, the 5FU should be withdrawn permanently.[1] Refer to Consultant.

Dose Modifications

Haematological Toxicity:	Neutrophils ≥ 1.5 x 10^9/l and Platelets ≥ 100 x 10^9/l	Proceed with treatment.
	Neutrophils 0.5 - 1.4 x 10^9/l or Platelets 75 - 99 x 10^9/l	Delay by 1 week*. Repeat FBC and, if within normal parameters, continue with full dose treatment.
	Neutrophils < 0.5 x 10^9/l or Platelets < 75 x 10^9/l	Delay by 1 week*. Repeat FBC and, if within normal parameters, continue with 80% doses of both cisplatin and 5FU.

If any episode of neutropenic sepsis, give all further cycles of chemotherapy with a 20% dose reduction of both cisplatin and 5FU.

*Cetuximab is not myelosuppressive and so may be continued during periods of mild myelosuppression, according to clinician preference.

Renal Impairment: NB. Cisplatin is both eliminated primarily (> 90%) in the urine and is itself nephrotoxic. If significant renal toxicity, this must be discussed with the Consultant.

GFR (ml/min)	Cisplatin Dose
≥ 60	Give 100% dose
45 - 59	Give 75% dose
44 – 20	Cisplatin contra-indicated Carboplatin AUC 5, administered in 250ml 5% Glucose over 30 minutes, may be substituted. It may be given according to this protocol, with however no requirement for pre- or post-hydration, nor fluid balance/urine monitoring
< 20	Carboplatin contra-indicated

Carboplatin dose should be calculated using the Calvert Formula:
Dose = Target AUC x (25 + GFR)

There is little data for cetuximab in patients with impaired renal function. However, dose adjustments would not be expected to be required.

Hepatic Impairment:

Moderate hepatic impairment	Reduce initial 5FU dose by 1/3
Severe hepatic impairment	Reduce initial 5FU dose by ½

Dose can be increased if no toxicity seen. If in doubt, check with Consultant.

There is little data for cetuximab in patients with impaired liver function. However, dose adjustments would not be expected to be required.

Cetuximab Rash:

At the first sign of ***any*** skin toxicity / acneiform eruption, **up to Grade 2** (papular eruption with or without pruritis, covering 10 - 30% of BSA)	• Ensure Pliazon is being used regularly. • Initiate doxycycline 100mg po once daily, to continue throughout while on cetuximab. • Oral antihistamine for relief of any itch. Analgesia may be of benefit.
Grade 3 acneiform eruption (eruption covering > 30% BSA with or without pruritis, ***or*** < 30% but with extensive super-infection)	• Cetuximab treatment must be interrupted until resolved to ≤ Grade 2. • Increase doxycycline dose to 100mg bd continuous and maintain this dose with all further cetuximab. • Oral antihistamine for relief of any itch. Analgesia may be of benefit. • Once rash resolved, resume cetuximab at: - full dose with 1st occurrence; - 80% dose with 2nd occurrence; - 60% dose with 3rd occurrence.
Grade 3 acneiform eruption not responding to doxycycline 100mg bd	• Switch to erythromycin 500mg po qds
Grade 4 (associated with extensive superinfection requiring IV antibiotics)	• Rarely seen. Cetuximab permanently discontinued. Consult with dermatologist.

Topical acne medications are **not** recommended. Use of topical antibiotics is not encouraged, and needs to be discussed with Microbiology first.

Other Toxicities: If Grade 3/4 mucositis, diarrhoea or PPE occurs, the dose of 5FU should be reduced by 20% in subsequent cycles.
If diarrhoea or mucositis persists despite the above dose reduction of 5FU, consider a dose reduction of cetuximab to 200mg/m^2 once weekly.

For Grade 2 + neurotoxicity or ototoxicity, switch from cisplatin to carboplatin.

References:
Vermorken, JB et al; NEJM 2008; 359 (11): 1116 - 1127
Rash advice adapted from HER1/EGFR Inhibitor Rash Management Forum, 2005
[1]No data, but as current practice in several private oncology centres.
Segaert, S et al; Ann Oncol 2005; 16: 1425 - 1433