CETUXIMAB, CISPLATIN & 5-FLUOROURACIL

First-line treatment for loco-regional or metastatic recurrence of SCC of Head & Neck after radical surgery or radiotherapy.

Individual funding must be obtained before treatment with cetuximab may start.

Drugs/Dosage:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Route</th>
<th>Day(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cetuximab</td>
<td>400mg/m² then 250mg/m²</td>
<td>IV</td>
<td>Day 1 of Cycle 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>once weekly throughout chemotherapy</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>80mg/m²</td>
<td>IV</td>
<td>Day 1*</td>
</tr>
<tr>
<td>5-Fluorouracil</td>
<td>1000mg/m²/24hr</td>
<td>IV</td>
<td>Day 1 – Day 4*</td>
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</table>

*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/m² IV monotherapy every 2 weeks until progressive disease

Other drugs:

Pre-emptive management for all patients starting cetuximab:
- Pliazion cream applied to face, hands, feet, neck, back and chest twice daily throughout treatment (available free of charge from nurse-led)
- 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 the weeks when chemotherapy is due.

Weekly cetuximab: loading dose given 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.

Cisplatin: 1 litre 0.9% Sodium Chloride + 20mmol KCl + 10mmol MgSO₄ 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 MgSO₄ IV over 2 hrs
500ml 0.9% Sodium Chloride IV or 500ml - 1 litre water orally over 1 hour
5 Fluorouracil continuous IV infusion over 4 days, given via CVC and ambulatory infusion device
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

Regular Investigations:
FBC Day 1
U&Es & LFTs Day 1
Ca²⁺ Day 1
Mg²⁺ Day 1, plus before each dose of cetuximab
EDTA Prior to 1ˢᵗ cycle

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/m² 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.\textsuperscript{1} Refer to Consultant.

**Dose Modifications**

Haematological

| 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.

<table>
<thead>
<tr>
<th>GFR (ml/min)</th>
<th>Cisplatin Dose</th>
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<tbody>
<tr>
<td>≥ 60</td>
<td>Give 100% dose</td>
</tr>
<tr>
<td>45 - 59</td>
<td>Give 75% dose</td>
</tr>
</tbody>
</table>
| 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.

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| Reason for Update: review of management of cetux rash | Approved by Consultant: Dr S Whitaker |
| Version: 3 | Approved by Lead Chemotherapy Nurse: P Deery |
| Supersedes: Version 2 | Date: 2.8.13 |
| Prepared by: S Taylor | Checked by: C Tucker |
Hepatic Impairment:

<table>
<thead>
<tr>
<th>Moderate hepatic impairment</th>
<th>Reduce initial 5FU dose by 1/3</th>
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</thead>
<tbody>
<tr>
<td>Severe hepatic impairment</td>
<td>Reduce initial 5FU dose by 1/2</td>
</tr>
</tbody>
</table>

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 pruritus, 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 pruritus, 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/m² 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
^No data, but as current practice in several private oncology centres.