REGIMEN TITLE: Cetuximab and radiotherapy in Head & Neck Carcinoma

Indication: Locally advanced Squamous Cell carcinoma of the Head & Neck originating in oropharynx, hypopharynx or larynx, stage III or IV disease In combination with radiotherapy

NICE Eligibilities: Karnofsky performance status score 90% or greater (related to prognosis- i.e. clinicians should be mindful of the need to secure equality of access to treatment for patients with disabilities).

Platinum-based chemoradiotherapy is contra-indicated (myelosuppression, hypersensitivity, grade 3 or more neuro-/ototoxicity)

Suitability for radiotherapy

Comments: Cetuximab plus radiation therapy should be used with caution if history of coronary artery disease, arrhythmias and congestive cardiac failure.

Regimen details:

Loading dose: Cetuximab 400mg/m² IV D1 (week 1)
Maintenance dose: Cetuximab 250mg/m² IV D1 (week 2. and then onwards once a week for a total of 8 weeks including the loading dose)

Loading dose is given 1 week before starting radiotherapy. Total radiation dose between 70-76.8 Gy (depending on fractionation) (once daily, twice daily or concomitant boost fractionations used-gstt regimen is 64-70Gy in 30-33 fractions over 35-40 days)

Administration:
Loading dose: Cetuximab 5mg/ml IV over 120 minutes
Maintenance dose: Cetuximab 5mg/ml IV over 60 minutes

Supplied neat in a sterilised 250ml empty infusion bag for infusion, or in a sterilised syringe for the syringe pump.

Cetuximab is administered intravenously with an infusion pump, gravity drip or a syringe pump. Maximum infusion rate must not exceed 10mg/min.

Availability of resuscitation equipment must be ensured, as anaphylactic reactions have been documented.

Patients should be observed during the infusion and at least 1 hour after the completion of the infusion for symptoms like fever and chills or other infusion-related symptoms (heart rate, blood pressure, temperature, respiration rate). Interruption and slowing down the infusion rate may help control such symptoms and infusion may be resumed when milder symptoms abate (see infusion related reactions- section below).
Cetuximab is administered before the same day’s fraction of radiotherapy, otherwise the timing between Cetuximab and radiotherapy is not critical. Radiotherapy dose should be administered at least one hour after cetuximab infusion ends.

Frequency: Weekly cycle, up to 8 weeks
Treatment to be continued during radiotherapy

Anti-emetics: Low emetogenicity

Regular investigations:
- FBC: Day 1
- LFTs: Day 1
- U&Es: Day 1
- Mg, Ca: Baseline and periodically until 8 weeks post therapy

Disease assessments: weeks 4 and 8, 4 monthly for 2 years, Then 6 monthly (CT/MRI, examinations, biopsies, imaging studies)

Supportive medication: Prophylactic chlorphenamine and corticosteroid to be given 30 minutes before infusion to prevent infusion related side-effects.

Extravasation: Non vesicant

Toxicities:
- Infusion related symptoms (mild to moderate in severity): fever, chills, nausea, vomiting, headache, dizziness, dyspnoea (occur mainly soon after the first infusion)
- Serious infusion related reactions/ anaphylaxis, Skin reactions (acne-like rash, dry skin, itching, nail changes), radiation dermatitis, mucositis, dry mouth, dysphagia, dyspnoea, electrolyte disturbances, increased liver enzymes, weight loss, hair loss (with radiotherapy)
- Adequate contraceptive methods should be used during therapy and at least 60 days following the last treatment dose.

Infusion related reactions
Majority occur during the first infusion. Mild or moderate symptoms may resolve following interruption of the infusion or decreasing the infusion time. Maintain the lower infusion rate in all subsequent infusions.

More severe infusion-related symptoms have also been reported, usually during the first infusion. The reactions may occur after several hours from administration (rare). Occurrence of a severe infusion related reaction requires immediate and permanent discontinuation of Cetuximab therapy and may necessitate emergency treatment.

Special attention is required for patients with reduced performance status and pre-existing cardio-pulmonary disease.
Respiratory disorders
Dyspnoea may occur as an immediate infusion related reaction, but has also been reported after several weeks of therapy. Advanced age, impaired performance status, and underlying cardiac/ pulmonary disorders may increase the risk of severe/ long-standing dyspnoea. Discontinue Cetuximab if interstitial lung disease is diagnosed.

Radiation dermatitis (see appendix 1, table 2.)
Radiation dermatitis usually appears within a few weeks of commencing radiotherapy. Management of radiation dermatitis (+/- co-existing cetuximab related skin rash), especially if grade ≥ 2 (see listings below and table 2, appendix 2), should be discussed in MDM comprising the radiation oncologist, wound care specialist nurse and dermatologist as needed. Skin reactions should be assessed at least once a week. Different irradiated areas may benefit from different topical treatment approaches; drying pastes for moist reactions within skin folds, hydrophilic dressings to provide symptomatic release, gels for seborrhoic areas and creams for areas outside skin folds and seborrhoic areas. Greasy topical products should be avoided because they inhibit the absorption of wound exudate and promote superinfection. Topical antibiotics should not be used prophylactically and should be reserved for superinfection.

Topical moisturisers, gels, emulsions or dressings should not be applied shortly before radiation treatment as they can cause a bolus effect, thereby artificially increasing the radiation dose to the epidermis. The skin in the radiation field should be cleaned and dried gently just prior to radiotherapy. The use of a pH neutral synthetic detergent is preferable to soap, which can irritate the skin.

Cetuximab treatment (as well as radiotherapy) may need to be interrupted if the patient develops a severe radiation reaction. Discuss with consultant in each individual case.

Definition of radiation dermatitis (*NCI CTCAE, v3.0)
Grade 1  Faint erythema or dry desquamation
Grade 2  Moderate to brisk erythema; patchy, moist desquamation, mostly confined to skin folds and creases; moderate oedema
Grade 3  Moist desquamation other than skin folds and creases; bleeding induced by minor trauma or abrasion
Grade 4  Skin necrosis or ulceration of full thickness of dermis; spontaneous bleeding from involved site

(*National Cancer Institute Common Terminology Criteria for Adverse Events)

Dose Modifications

Haematological Toxicity
Cetuximab has not been studied in patients with pre-existing haematological disorders. Generally Cetuximab is not myelosuppressive and the treatment may continue during periods of mild myelosuppression. Discuss with consultant if concerned.

FBC
Neut ≥ 1.5 x 10^9/L, Plats ≥ 100 x 10^9/L  Cetuximab
100% dose
Renal Impairment
Only patients with adequate renal function have been investigated to date.
CrCl > 60ml/min 100% dose
CrCl < 60ml/min Discuss with consultant

Hepatic Impairment
Only patients with adequate hepatic function have been investigated to date.
Bili ≤ 2.0 mg/dl and/or AST/ALT ≤ 3 x ULN 100% dose
Bili > 2.0 mg/dl and/or AST/ALT > 3 x ULN Discuss with consultant

Non-haematological toxicity
Cetuximab is recommended to be discontinued in grade 3 or 4 hypersensitivity reactions.
Do not delay Cetuximab in radiation related toxic effects, or do not delay radiotherapy in Cetuximab related toxicity.

Cetuximab related skin reactions
Cetuximab related acne-like rash in patients on concurrent radiotherapy typically appears within irradiated fields approximately 3 to 5 weeks after initiation of treatment. Management of acniform rash co-existing with radiation dermatitis within irradiated fields when grade ≥ 2 should follow the management of radiation dermatitis.

Beneficial treatment approaches for cetuximab related skin reactions (also outside irradiated fields) include topical anti-inflammatory or antibiotic medication, oral tetracyclines for grade 2+ (lesions with symptoms, intervention indicated) reactions with sufficient cover for Staphylococcus aureus superinfection when necessary, and oral antihistamines for pruritus. The long-term use of corticosteroids is generally avoided due to their potential to induce or exacerbate acne and other skin conditions and to interfere with the antibody-dependent cell-mediated cytotoxicity reactions thought to contribute to the antitumour effects of cetuximab.

Cetuximab dosing in severe skin reactions:
Interrupt Cetuximab in severe skin reactions (grade 3 or more acniform rash). Treatment may only be resumed if the reaction has resolved to grade 2.

Grade 3 or more acniform rash Cetuximab continuation dose after resolving to grade 2.
First occurrence 100% previous dose
2nd occurrence reduce from 250mg/m² to 200mg/m²
3rd occurrence reduce from 200mg/m² to 150mg/m²
Discontinue Cetuximab permanently in 4th occurrence of severe skin toxicity.

Cetuximab causes sun-sensitivity that may exacerbate skin reactions. Protect from sun.

Drug interactions: No documented interactions

References:
NICE FAD 145
S.Segaert et al. (2005) Ann Oncol; 16(9):1425-1433
www.medicines.org.uk, accessed Dec 08
CCO Formulary. Revised July 07
Micromedex review, July 08
<table>
<thead>
<tr>
<th>BSA</th>
<th>Loading dose (400mg/m²)</th>
<th>Maintenance dose (250mg/m²)</th>
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<tbody>
<tr>
<td></td>
<td>mg ml</td>
<td>mg ml</td>
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<tr>
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<td>480  96</td>
<td>300  60</td>
</tr>
<tr>
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<tr>
<td>2.2</td>
<td>880 176</td>
<td>550 110</td>
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</table>
### Table 2. Grade-specific management of radiation dermatitis in patients with squamous cell carcinoma of the head and neck receiving radiotherapy and cetuximab

<table>
<thead>
<tr>
<th>Grade of radiation dermatitis</th>
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<th>Grade 1</th>
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<th>Grade 3</th>
<th>Grade 4</th>
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<tr>
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</tr>
</tbody>
</table>

**General management**
- Radiotherapy technique, Dose and distribution
- Medication review
- Skin preparation
- Maintain hygiene and gently clean and dry skin in the radiation field shortly before radiotherapy
- They can cause a bolus effect, thereby artificially increasing the radiation dose to the epidermis

**Grade specific management**
- Use of moisturiser
  - optional
- If anti-infective measures are desired, antibacterial moisturisers may be used occasionally

**Management team**
- Primarily nursing staff

**Topical creams and dressings following radiotherapy**
- Drying gels, possibly with the addition of antiseptics
- an anti-inflammatory emulsion
- hydrophilic dressings, applied after radiotherapy to the cleaned, irradiated area, for symptomatic relief
- zinc oxide paste, if easy to remove prior radiotherapy
- when used, silver sulfadiazine or beta glucan cream should be applied after radiotherapy (possibly in the evening) after cleaning the irradiated area

**Where infection is suspected**
- treating physicians best clinical judgement for identifying infection, consideration For swabbing the area for identification of the infectious agent
- topical antibiotics (should not be used prophylactically)
- doxycycline is not recommended at this stage
- blood granulocyte counts should be checked, particularly if on concomitant chemotherapy
- blood cultures if additional signs of sepsis and/or fever

**Management team**
- Integrated management team comprising the radiation oncologist, nurse, Medical oncologist (where appropriate) and dermatologist, as required
- Skin reactions should be assessed at least once a week

**Reason for Update:** Updated SPC  
**Version:** 2  
**Supersedes:** Date: 3/3/09  
**Prepared by:** S. Eestila Dec08  
**Checked by:** (Network Pharmacist): J. Turner  
**Approved by SELCN DTAC Chair:** Nic Ketley Date: 4th March-09