CETUXIMAB in colorectal cancer

Indication:
NICE

NICE Approved as 1st line for EGFR-expressing KRAS wild type metastatic colorectal cancer, when all of the following criteria are met:

**Cetuximab in combination with Irinotecan & Modified de Gramont, or with Oxaliplatin & Modified de Gramont.**

NICE criteria to be met:
- The primary tumour has been resected or is potentially operable
- The metastatic disease is confined to the liver and is unresectable
- The patient is fit enough to undergo surgery to resect the primary colorectal tumour and to undergo liver surgery if the metastases become resectable after treatment with cetuximab
- Treatment with cetuximab is for no more than 16 weeks
- The manufacturer rebates 16% of the amount of cetuximab used on a per patient basis, when used in combination with Oxaliplatin based regimen (please refer to documentation in the manufacturer’s patient access scheme)

CDF

Treatment of EGFR-expressing KRAS wild type metastatic colorectal cancer that has progressed after first line chemotherapy, or are continuing first line treatment with Cetuximab beyond NICE approved 16 weeks (see above).

**Cetuximab in combination with Irinotecan (refer to separate Irinotecan protocol), or As a single agent in patients who have failed oxaliplatin – and irinotecan-based therapy and who are intolerant to irinotecan.**

LCNDG criteria to be met:
- Histologically confirmed Colorectal adenocarcinoma
- Stage IV (metastatic) disease
- Progression of disease with prior chemotherapy
- Cetuximab has not been given in the first line setting for metastatic disease
- Positive mutational analysis for KRAS-wild type, using a validated test method
- Karnofsky PS 60% or more

Ensure funding has been confirmed according local arrangements.

Drugs/Dosage:

**Weekly administration:**

- **Cetuximab loading dose**: 400mg/m² IV D1 (week 1)
- **Cetuximab maintenance dose**: 250mg/m² IV D1 (week 2 onwards)

Once a week, until progression

Consider reloading with Cetuximab if treatment interrupted for more than 4 weeks

**2-weekly administration:**

- **Cetuximab**: 500mg/m² IV D1

2 weekly, until progression
Administration:

- **Cetuximab loading dose** and 2-weekly dose:
  - **Dosage:** 5mg/ml
  - **Route:** IV over 120 minutes
- **Cetuximab maintenance dose**:
  - **Dosage:** 5mg/ml
  - **Route:** 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).

When concomitant chemotherapy is given with Cetuximab, allow one hour before starting chemotherapy following Cetuximab dose.

**Frequency:**

- Weekly or 2-weekly administration (see above),
- **NICE:** 16 weeks only (including the loading dose)
- **CDF:** until progression

**Main Toxicities:**

**Cetuximab:** 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, hypomagnesaemia (very common) electrolyte disturbances, increased liver enzymes, weight loss, cardiovascular disorders

In combination with fluoropyrimidines, the frequency of **cardiac ischaemia including myocardial infarction and congestive heart failure** as well as the frequency of **hand-foot syndrome (palmar-plantar erythrodysaesthesia)** were increased compared to that with fluoropyrimidines alone.

**Anti-emetics:**

- Low emetogenicity

**Supportive medication:**

Prophylactic chlorphenamine + corticosteroid to be given 30 minutes before cetuximab infusion to prevent infusion related side-effects.

Loperamide tablets 4mg stat, then 2mg prn for diarrhoea

**Extravasation:**

- Non-vesicant

**Regular investigations:**

- **FBC**
- **U&E**
- **LFT**
- **Mg, Ca** Baseline and periodically until 8 weeks post therapy
- **CEA** 4 weekly
- **CT scan** after 12 weeks of treatment

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**Reason for Update:** SELCN ICDF guidance

**Approved by Consultant:** Nick Maisey

**Version:** 1

**Date:** 08/09/2011

**Supersedes:** All other versions

**Checked by (Network Pharmacist):** J.Turner

**Prepared by:** SEestilä Oct-10

**Date:** 08/2011
*Note: *When Cetuximab is given as a single agent until progression, the blood profile is recommended to be assessed 4 weekly.

### Toxicities and Dose Modifications

**Renal Impairment**

Before every cycle, calculate CrCl using Cockcroft and Gault. If borderline, an EDTA should be requested. Deteriorating organ function may be a sign of disease progression, therefore always discuss with the consultant. There is little experience of administering cetuximab in patients with renal insufficiency. No specific guidelines are available, however the major route of clearance is thought to be by internalisation & degradation of EGFR complex.

<table>
<thead>
<tr>
<th>CrCl (ml/min)</th>
<th>Cetuximab Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 30</td>
<td>100% dose</td>
</tr>
</tbody>
</table>

**Hepatic Impairment**

Deteriorating organ function may be a sign of disease progression, and require cessation of, or change in, treatment, therefore always discuss with the consultant. There is little experience of administering cetuximab in patients with hepatic insufficiency. No specific guidelines are available, however the major route of clearance is thought to be by internalisation & degradation of EGFR complex.

<table>
<thead>
<tr>
<th>Liver Function</th>
<th>Cetuximab Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bili &lt; 3 x ULN and/or ALT/AST &lt; 2.5 x ULN</td>
<td>100% dose</td>
</tr>
</tbody>
</table>

**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.

In combination with platinum-based chemotherapy, the frequency of severe leukopenia or severe neutropenia may be increased, and thus may lead to a higher rate of infectious complications such as febrile neutropenia, pneumonia and sepsis compared to platinum-based chemotherapy alone.

**Severe skin reactions:**

Acneiform/ papulopustular rash occurs in over 70% of patients. Usually occurs on the face, upper chest & back with multiple follicles & pustules. Onset is usually within the first 3 weeks.

Cetuximab dosing after severe skin reaction:

Interrupt Cetuximab in severe skin reactions (grade 3 or more acneiform rash). Discontinue cetuximab in the event of 3 consecutive weeks of non-resolving grade 3 toxicity.

<table>
<thead>
<tr>
<th>Grade 3 or more skin rash</th>
<th>Cetuximab continuation dose after resolving to grade 2.</th>
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<tbody>
<tr>
<td>First occurrence</td>
<td>100% previous dose</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; occurrence</td>
<td>reduce to 80% dose from initial</td>
</tr>
<tr>
<td>3&lt;sup&gt;rd&lt;/sup&gt; occurrence</td>
<td>reduce to 75% dose from initial</td>
</tr>
<tr>
<td>4&lt;sup&gt;th&lt;/sup&gt; occurrence</td>
<td>Discontinue Cetuximab permanently</td>
</tr>
</tbody>
</table>
Management recommendations for skin toxicities:

<table>
<thead>
<tr>
<th>Mild (grade 1) localised reaction with no associated physical symptoms</th>
<th>Moderate (grade 2) more disseminated reaction, can include tenderness and/or pruritus</th>
<th>Severe (grade 3) major symptoms affecting activities of daily living, intolerable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continue Cetuximab</td>
<td>Continue Cetuximab, consider dermatology advice</td>
<td>Hold Cetuximab (see above), refer to the dermatology for advice/management</td>
</tr>
<tr>
<td>Topical low/medium potency corticosteroids (hydrocortisone 1%) as pulsed therapy, or</td>
<td>Topical low/medium potency corticosteroids (hydrocortisone 1% or 2.5%) and/or</td>
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</tr>
<tr>
<td>Topical antibacterial (clindamycin 1%)</td>
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</tr>
<tr>
<td>Consider course of oral tetracyclines (doxycycline 100mg od)</td>
<td>4 weeks course of oral tetracyclines (doxycycline 100mg od-bd)</td>
<td>4 weeks course of oral tetracyclines (doxycycline 100mg od-bd)</td>
</tr>
<tr>
<td>Assess 2 weekly, if worsens or does not improve, proceed to next step</td>
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<td>Consider additional short course of oral corticosteroid (empirical)</td>
</tr>
</tbody>
</table>

If pruritus occurs an oral antihistamine is advised. Dry skin often occurs (and may contribute to pruritus) general advice on replacing soap with oil for washing, avoidance of hot water for baths or showers and regular use of emollient creams are beneficial. Cetuximab causes sun-sensitivity that may exacerbate skin reactions. Protect from sun. Advise use of sunscreens with SPF ≥ 15. Avoid over-the-counter acne medications, as these may worsen the rash.

**Infusion related reactions**

Majority occur during the first infusion. Mild or moderate symptoms may resolve following interruption of the infusion or increasing the infusion time. Maintain the lower infusion rate in all subsequent infusions (see below). 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 (see below).
<table>
<thead>
<tr>
<th>CTC Grade</th>
<th>Allergic/hypersensitivity reaction</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>Transient flushing or rash, drug fever &lt;38°C</td>
<td>Decrease the cetuximab infusion rate by 50% and monitor closely for any worsening. The total infusion time for cetuximab should not exceed 240 minutes.</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Rash; flushing; urticaria; dyspnea; drug fever ≥ 38°C</td>
<td>Stop cetuximab infusion. Administer bronchodilators, oxygen etc. as medically indicated. Resume infusion at 50% of previous rate once allergic/hypersensitivity reaction has resolved or decreased to grade 1 in severity, and monitor closely for any worsening.</td>
</tr>
<tr>
<td>Grade 3 or Grade 4</td>
<td></td>
<td>Stop cetuximab infusion immediately and disconnect infusion tubing from the patient. Administer adrenaline, bronchodilators, antihistamines, glucocorticoids, intravenous fluids, vasopressor agents, oxygen etc., as medically indicated. Patients have to be withdrawn immediately from treatment and must not receive any further cetuximab.</td>
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</tbody>
</table>

**Other Non-Haematological Toxicities**

Consider dose reducing cetuximab to 200mg/m² if symptoms persist.

Cetuximab is recommended to be discontinued in grade 3 or 4 hypersensitivity reactions.

**Hypomagnesaemia** is very common. Fatigue, malaise, tremor, ataxia, carpopedal spasm, hyperreflexia, confusion, hallucinations, convulsions and arrhythmias may occur. ECG changes include prolonged QT interval and broad flattened T waves. Patients with marked hypomagnesaemia (Mg less than 0.4mmol/L) require ECG and intravenous administration of magnesium. Secondary hypokalaemia & hypocalcaemia may also occur. Hypomagnesaemia should be corrected by intravenous supplementation if grade 3 (<0.4mmol/L) or if symptomatic. If lesser degrees of hypomagnesaemia are detected, oral supplementation may be considered. A suitable preparation is magnesium glycerophosphate (unlicensed).

If Magnesium fails to rectify on magnesium supplementation, it may also be necessary to supplement calcium.

**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.

**Nail toxicities** occur in 8% of patients characterised by a paronychial inflammation with associated swelling of the lateral skin folds of toes and fingers, especially great toes and thumbs, which may be painful. It may persist for up to three months after cessation of cetuximab therapy. Dermatological advice should be sought.
References:

www.medicines.org.uk,
www.micromedex.com
NICE documentation
ICDF SELCN documentation, Oct 2010
Rash advice:
Melosky et al. Current oncology, BCCA practise guideline series (2009);16(1)
Saif et al. JOP (2010);11(2):176-182
Perez-Soler et al. The Oncologist (2005);10:345-356