CETUXIMAB + OXALIPLATIN MdG

First-line treatment of EGFR-expressing RAS wild type metastatic colorectal cancer

Blueteq registration is required before cetuximab treatment may start

Drugs/Dosage:

Cetuximab	500mg/m^2	IV	Day 1
Calcium folinate	350mg	IV	Day 1
Oxaliplatin	85mg/m^2	IV	Day 1
5-Fluorouracil	400mg/m^2	IV	Day 1
5-Fluorouracil	2400mg/m^2	IVI	over 46 hrs, starting Day 1

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)
- 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 dex will not be needed pre-chemotherapy

Administration:

Cetuximab must be administered before chemotherapy. The first cetuximab dose is to be given over 120 minutes. If the 1st dose is tolerated, all subsequent doses to be given over 90 minutes.
After doses 1 and 2 of cetuximab, patients need to be observed for one hour to ensure no delayed reaction, and 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.
Oxaliplatin in 250ml 5% glucose 5% over 2 hours
concurrently with
Calcium folinate in 250ml glucose 5% over 2 hours
Flush with glucose 5%, and then give 5FU bolus injection over 5 minutes
5FU infusion via central venous catheter and ambulatory infusion device over 46 hours

Frequency:

Every 2 weeks
Duration of treatment is patient- and Consultant-dependent, with options including: treatment to progression; or 3 to 6 month blocks of treatment, followed by a drug holiday or less intensive regimen, for patients who have responded, or have stable disease.
However, cetuximab may not continue after a *planned* treatment break.
If being used neo-adjuvant to complete resection of metastases, cetuximab is to be discontinued after surgery (adjuvant chemotherapy alone to be used post resection)

Main Toxicities:

myelosuppression; mucositis; diarrhoea; neurotoxicity (see Comments); allergic infusion-related reactions to cetuximab and oxaliplatin (see Comments); coronary artery spasm (see Comments); palmar/plantar erythema; skin reactions to cetuximab (acne-like rash, dry skin, itching, nail changes); sore eyes; hypomagnesaemia; ovarian failure/infertility

Reason for Update: indication updated following NICE TA	Approved by Consultant: Dr S Essapen
Version:	Approved by Lead Chemotherapy Nurse:
Supersedes: Version 5	Date: 7.7.17
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Anti-emetics:	Day 1: highly emetogenic	
Regular Investigations:	FBC	Day 1
	U&Es & LFTs	Day 1
	Mg^{2+}	Day 1
	CEA	every 4 weeks
	CT scan	baseline, then every 8 weeks

Comments:

Oxaliplatin & Acute Cold-related Dysaesthesia (CRD):
Many patients experience transient paraesthesia of hands & feet, and some experience laryngopharyngeal dysaesthesia (unpleasant sensations in the throat). Onset is during or within hours of infusion, and resolves within minutes to a few days. Symptoms are exacerbated by cold, so patient should be well advised on precautions to be taken. Does not require treatment or dose reduction.
For laryngopharyngeal dysaesthesia, subsequent infusions should be given over 6 hours. Consideration to infusion of 10mmol of magnesium + 1gram of calcium gluconate in 0.9% sodium chloride 250ml over 1 hour, prior to starting the oxaliplatin, should also be made.
NB. The above management should **not** be used to try and alleviate CRD or cumulative neuropathy.

Oxaliplatin & Cumulative dose related peripheral sensory neuropathy:
Usually occurs after a cumulative dose of 800mg/m^2. It can occur after treatment with oxaliplatin is completed, and is usually reversible, taking approx 3 – 5 months to recovery.

Allergic reactions to oxaliplatin during infusion: Immediate intervention is to stop the infusion and call for medical help. Treat with IV corticosteroid and antihistamine. After full recovery, the patient may continue with folinic acid and 5FU.
At Consultant discretion, the patient may be re-challenged with oxaliplatin, according to the grade of reaction, as detailed in the separate document "Oxaliplatin Hypersensitivity & desensitisation regimen".

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.

Low magnesium is to be treated according to local guidelines.

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 or Platelets < 75 x 10^9/l	Delay chemotherapy* for 1 week or until FBC recovered. If any Grade 3 or 4 neutropenia (< 1.0 x 10^9/l) or thrombocytopenia (< 50 x 10^9/l) observed, reduce oxaliplatin to 65mg/m^2 and reduce 5FU (bolus & infusion) by 20%.

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

Renal Impairment: Cockcroft & Gault formula may be used to predict creatinine clearance. If borderline, or if predicted renal function falls by > 30%, an EDTA should be requested.

CrCl (ml/min)	Oxaliplatin Dose	5 Fluorouracil Dose
≥ 30	Give 100% dose	Give 100% dose
< 30	Omit oxaliplatin	Give 75% dose

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

Hepatic Impairment:

Liver Function	Oxaliplatin Dose	5 Fluorouracil Dose
*Bilirubin > 3 x ULN	Give 50% dose	Give 50% dose

*Note that significantly impaired hepatic function may be a sign of disease progression and require cessation of, or change in, treatment. **Always discuss deteriorating organ function 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; - 400mg/m^2 with 2nd occurrence; - 300mg/m^2 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.
Neurological Toxicity:	If neurological symptoms occur, use the following oxaliplatin dose adjustment guidelines: Symptoms lasting > 7 days and troublesome; reduce oxaliplatin dose to 65mg/m^2. Paraesthesia without functional impairment persisting until next cycle; reduce oxaliplatin dose to 65mg/m^2. Paraesthesia with functional impairment persisting until the next cycle; oxaliplatin should be discontinued. (Re-initiation may be considered if symptoms resolve)
Stomatitis:	For stomatitis occurring between cycles, treat symptomatically. Further chemotherapy must be delayed until fully resolved. If mouth ulcers develop, reduce the 5FU doses (bolus and infusion) by 20% for subsequent cycles. If further toxicity occurs, reduce the 5FU bolus and infusion by a further 20%, and also reduce the oxaliplatin dose by 20%. If mucositis persists despite the recommended dose reductions of chemotherapy, consider a dose reduction of cetuximab to 400mg/m^2 every 2 weeks.
Diarrhoea:	For diarrhoea occurring between cycles, treat symptomatically. If diarrhoea has not resolved by the time the next cycle is due, delay 1 week. For any Grade 3 diarrhoea or stomatitis, reduce subsequent 5FU doses (bolus and infusion) by 20%. For any Grade 4 diarrhoea, or repeated Grade 3 after 5FU dose reduction, also reduce the oxaliplatin to 65mg/m^2 for subsequent cycles. If diarrhoea persists despite the recommended dose reductions of chemotherapy, consider a dose reduction of cetuximab to 400mg/m^2 every 2 weeks.
Palmar/Plantar Erythema:	Treat symptomatically, initially with pyridoxine 50mg po tds. If Grade 3 or 4 PPE occurs, delay further treatment until Grade 0 – 1 and then reduce the 5FU (bolus and infusion) by 20% for subsequent cycles.
References:	Van Cutsem, E et al; NEJM 2009; 360: 1408 – 1417 Bokemeyer, C et al; JCO 2009; 27 (5): 663 - 671 Bechstein, W et al; ASCO Proceedings 2009, Abstract No 4091 Rash advice adapted from HER1/EGFR Inhibitor Rash Management Forum, 2005 Tabernero, J et al; JCO 2006; 24 (18 suppl): 142s: abstract 3085 (2-weekly cetux)