Cetuximab, Carboplatin and Fluorouracil

Indication

Treatment of recurrent or metastatic squamous cell carcinoma of the head and neck for oral cavity primaries and where cisplatin is contraindicated. WHO performance status 0-1.

NICE TA473

ICD-10 codes

Codes prefixed with C00-C13

Regimen details

In combination with chemotherapy

Day	Drug	Dose	Route
1 (loading dose)	Cetuximab	400mg/m^2	IV infusion
Then weekly maintenance dose (i.e. days, 8, 15 and day 1, 8 and 15 of subsequent cycles)	Cetuximab	250mg/m^2	IV infusion
1	Carboplatin	AUC 5	IV infusion
1-4*	Fluorouracil	1000mg/m^2/day	Continuous IV infusion

* 4 days of treatment, commencing day 1 and finishing day 5

The carboplatin dose is calculated using the Calvert equation: **Carboplatin dose (mg) = AUC (CrCl +25)**
Creatinine clearance (CrCl) is calculated using the Cockcroft and Gault equation, however for patients where the creatinine level may not truly reflect renal function (e.g. in extremes of BSA or debilitated patients) a nuclear medicine GFR should be performed.
CrCl should be capped at 125mL/min

Cetuximab maintenance - two-weekly regimen*

Day	Drug	Dose	Route
1	Cetuximab	500mg/m^2	IV infusion

* Note: this dosing regimen is unlicensed.

Cycle frequency

21 days
14 days maintenance

Number of cycles

Up to 6 cycles.
Maintenance cetuximab in patients with ongoing stable disease or response after 6 cycles – continue until disease progression.

Administration

Loading dose: Cetuximab is administered as an intravenous infusion over 120 minutes (maximum infusion rate must not exceed 5mg/min).
Maintenance dose: Cetuximab is administered as an intravenous infusion over 60 minutes (maximum infusion rate must not exceed 10mg/min).

Cetuximab is supplied undiluted at a concentration of 5mg/mL in an empty infusion bag.

Patients should be observed for fever and chills and other symptoms of infusion-related reaction during and for at least 1 hour after the completion of the infusion (heart rate, blood pressure, temperature, respiration rate should be taken prior to commencing infusion, at 30 minutes and post infusion). Interruption and slowing down the infusion rate may help control such symptoms. Chemotherapy must not be administered less than 1 hour after completion of cetuximab infusion.

If a mild or moderate infusion-related reaction occurs, the infusion may be resumed once the symptoms abate. It is recommended to maintain the lower infusion rate for subsequent infusions.

Severe infusion-related reactions have been documented and require immediate and permanent discontinuation of cetuximab therapy and may necessitate emergency treatment. Resuscitation equipment must be available during administration

Carboplatin is administered in 250-500mL glucose 5% over 30-60 minutes.

Patients should be observed closely for hypersensitivity reactions, particularly during the first and second infusions.

Fluorouracil is administered by continuous infusion via ambulatory pump over 4 days (96 hours) or by IV infusion in 1000mL sodium chloride 0.9% over 22 hours each day for 4 days.

Pre-medication

The following should be administered 30 minutes prior to each dose of cetuximab:

- Chlorphenamine 10mg IV
- Ranitidine 150mg PO/PEG
- Dexamethasone 8mg IV
- Paracetamol 1g PO/PEG

Ensure regular use of moisturiser. Additional medication may be required for skin toxicities, as per guidelines below.

Emetogenicity

This regimen has a moderate emetogenic potential, maintenance cetuximab has low emetic potential.

Additional supportive medication

Mouthwashes as per local policy.
H_2 antagonist or proton-pump inhibitor if required.
Loperamide if required.
Doxycycline, emollient cream / wash as prophylaxis against cetuximab induced skin toxicities
See below for guidelines for further management of cetuximab induced skin toxicities.
Oral magnesium supplementation between cycles in addition to the intravenous magnesium administered at the time of chemotherapy if required (see below).

Extravasation

Cetuximab is neutral (Group 1)
Carboplatin is an exfoliant (Group 3).
Fluorouracil is an inflammatant (Group 2).

Investigations – pre first cycle

Investigation	Validity period (or as per local policy)
FBC	14 days
U+E (including creatinine)	14 days
LFTs	14 days
Magnesium	14 days

Consider formal measurement of GFR.

Investigations – pre subsequent cycles

Investigation	Validity period (or as per local policy)
FBC	96 hours
U+E (including creatinine)	7 days
LFTs	7 days
Magnesium	7 days

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant.

Investigation	Limit
Neutrophils	≥ 1.5 x 10^9/L
Platelets	≥ 100 x 10^9/L
AST/ALT	≤ 1.5 x ULN
Alkaline Phosphatase	≤ 2.5 x ULN
Creatinine Clearance (CrCl)	> 30mL/min
Magnesium	≥ 0.7 mmol/L (see below for replacement)

Dose modifications

For non-haematological toxicity (except alopecia) delay treatment until resolved to ≤ grade 1 and discuss with consultant.

- **Haematological toxicity**

Defer treatment for 1 week if neutrophil count <1.5 x 10^9/L and/or platelets <100 x 10^9/L.

If delayed on two occasions or grade 3 haematological toxicity reduce carboplatin dose to AUC 4 and fluorouracil to 80% for all future cycles.

If grade 4 haematological toxicity discontinue treatment.

Cetuximab may be continued, discuss with consultant.

- **Renal impairment**

CrCl (mL/min)	**Carboplatin dose**
> 30	100%
20-30	EDTA formal measurement of GFR) then 100% dose
< 20	Omit

If CrCl falls by more than 10% from the previous cycle then consider a dose reduction.

Consider dose reduction of fluorouracil dose only in severe renal impairment – discuss with consultant

There is little experience of administering cetuximab in patients with renal impairment. Discuss with consultant if CrCl <30ml/min.

- **Hepatic impairment**

AST/ALT (x ULN)		**Alkaline Phosphatase** (x ULN)	**Fluorouracil dose**
≤ 1.5	and	≤ 2.5	100%
>1.5 - ≤ 3.5	and/or	> 2.5 -≤ 6	Start at 80%*
> 3.5	and/or	> 6	Discuss with consultant. Usually start at 50% if no other toxicity*

*Fluorouracil can be increased if no toxicity.

Transient increases in liver enzymes have been seen in patients being treated with carboplatin although no dose reduction is usually required. If bilirubin ≥ 3 x ULN and/or transaminases ≥ 5 x ULN discuss with consultant.

No hepatic function dose modifications are required for cisplatin or cetuximab however if AST/ALT > 3xULN or bilirubin > ULN discuss with consultant.

- **Other toxicities**

Toxicity	**Definition**	**Dose adjustment**	
		Fluorouracil	**Carboplatin**
Diarrhoea	Grade 1: Manage symptomatically with loperamide +/or codeine phosphate	100%	100%
	Grade 2: 2nd occurrence	80%	100%
	Grade 3: 1st occurrence	80%	100%
	Grade 3: 2nd occurrence	50%	80%
	Grade 4: 1st occurrence	Discontinue treatment	
Stomatitis/Mucositis	Grade 1: Manage symptomatically with mouthwashes	100%	100%
	Grade 2: 2nd occurrence	80%	100%
	Grade 3: 1st occurrence	80%	100%
	Grade 3: 2nd occurrence	50%	80%
	Grade 3: 3rd occurrence	Discontinue treatment	
	Grade 4: 1st occurrence	Discontinue treatment	
Hypomagnesaemia	<0.4mmol/L or 0.4 - 0.6 mmol/L (symptomatic)	IV Magnesium Sulphate 4g in 1000mL sodium chloride 0.9% over 4 hours	
	0.4 – 0.6 mmol/L (asymptomatic)	Oral supplementation unless contraindicated	
	NB Magnesium salts should be taken with food to minimise diarrhoea.		

Dose reductions for stomatitis or diarrhoea are based on the dose given in the preceding cycle and continue for remaining cycles. If multiple toxicities, the dose administered is based on the most severe toxicity experienced.

If ≥ grade 2 stomatitis or diarrhoea, fluorouracil must not be given. Treatment must be deferred one week until toxicity has resolved to ≤ grade 1 toxicity.

Skin reactions

For any grade of skin reaction despite prophylactic doxycycline and emollient follow the guidelines below:

- Ensure regular use of moisturiser and use of emollient cream in place of soap to wash
- 1% clindamycin lotion to pustules
- 1% Hydrocortisone cream for pruritus
- Oral antihistamine for pruritus
- If ≥ grade 2 consider increasing doxycycline to 100mg BD until improves

- If ≥ grade 3 suspend until resolution ≤ grade 2 and increase doxycycline to 100mg BD to continue throughout treatment (if ≥ grade 3 and if no response consider switching to erythromycin 500mg QDS and oral prednisolone 30mg OM for 7 days, then reducing by 5 mg per day before stopping)

Interrupt cetuximab in severe skin reactions (≥ grade 3 acneiform rash). Treatment may only be resumed if the reaction has resolved to grade 2, according to the dosing table below:

≥ Grade 3 acneiform rash	**Cetuximab dose after resolution to ≤ grade 2**
1st occurrence	100% previous dose
2nd occurrence	Reduce from 250 mg/m^2 to 200 mg/m^2
3rd occurrence	Reduce from 200 mg/m^2 to 150 mg/m^2
4th occurrence	Discontinue permanently

If the skin reaction does not resolve to ≤ grade 2, treatment should be discontinued.

Discontinue treatment if interstitial lung disease is diagnosed.

Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects**

Myelosuppression
Cardiac toxicity including coronary vasospasm
S.aureus super-infection
Hypersensitivity reactions
Diarrhoea

- **Frequently occurring side effects**

Myelosuppression
Nausea and vomiting
Diarrhoea or constipation
Stomatitis and mucositis
Palmar-plantar erythema
Alopecia (mild)
Rash
Electrolyte imbalances
Loss of appetite, taste alterations
Fatigue
Sore eyes and runny nose
Onychonychia

Significant drug interactions – for full details consult product literature/ reference texts

Folinates: Avoid concomitant use of folinic and folic acid – enhanced toxicity of fluorouracil.
Co-trimoxazole/trimethoprim: Avoid if possible – enhances antifolate effect. If essential, monitor FBC regularly.
Warfarin/coumarin anticoagulants: Avoid use due to elevations in INR. Switch to low molecular weight heparin during treatment.
Aminoglycoside antibiotics: increased risk of nephrotoxicity and ototoxicity
Clozapine: increased risk of agranulocytosis, avoid concomitant use
Diuretics: increased risk of nephrotoxicity and ototoxicity
Nephrotoxic drugs: increased nephrotoxicity ; not recommended
Phenytoin: carboplatin reduces absorption and efficacy of phenytoin

Additional comments

Dihydropyrimidine dehydrogenase (DPD) deficiency as a result of polymorphism variants in the DPYD gene can result in severe toxicity secondary to reduced fluorouracil metabolism. This is common; present 3-6% of population and results in severe myelosuppression, diarrhoea and/or stomatitis. In patients with combined DPYD gene polymorphism variants that result in no DPD production toxicities are frequently fatal. **All patients should be tested for the most common DPYD variants prior to commencing 5FU** (or as per local guidance).

Cardiotoxicity has been associated with fluoropyrimidine therapy, with adverse events being more common in patients with a prior history of coronary artery disease. Caution must be taken in patients with a history of significant cardiac disease, arrhythmias or angina pectoris.

Hypersensitivity reactions may occur due to cetuximab, cisplatin or mannitol.

Cetuximab should be used with caution in patients with active peripheral, cerebral or coronary vascular disease or any form of myelosuppression.

It is recommended to warn patients of the possibility of late onset infusion reactions and instruct them to contact their doctor/nurse team if symptoms of an infusion-related reaction occur. If severe, a reaction requires immediate and permanent discontinuation of cetuximab therapy and may necessitate emergency treatment.

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

References

- National Institute for Clinical Excellence (TA 473) accessed 26 June 2019 via www.nice.org.uk
- Summary of Product Characteristics Carboplatin (Hospira) accessed 26 June 2019 via www.medicines.org.uk
- Summary of Product Characteristics Fluorouracil (Hospira) accessed 26 June 2019 via www.medicines.org.uk
- Summary of Product Characteristics Cetuximab (Merck Serono) accessed 26 June 2019 via www.medicines.org.uk
- Segaert, S et al; Clinical signs, pathophysiology and management of skin toxicity during therapy with epidermal growth factor receptor inhibitors. Ann Oncol 2005; 16: 1425 – 1433
- Vermorken, JB et al; Platinum-Based Chemotherapy plus Cetuximab in Head and Neck Cancer. NEJM 2008; 359 (11): 1116 - 1127

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