

Cetuximab, Carboplatin and Fluorouracil (Head and Neck)

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

Cycle 1:

Day	Drug	Dose	Route
1 (loading dose)	Cetuximab	400mg/m ²	IV infusion
8 & 15	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

All patients must have documented DPYD status and fluorouracil doses adjusted accordingly prior to commencing treatment as per local practice.

Subsequent cycles:

Day	Drug	Dose	Route
1, 8 and 15	Cetuximab	250mg/m ²	IV infusion
1	Carboplatin	AUC5	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

Combination cycles: 21 days

Maintenance cetuximab: 14 days

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 (NB. maximum infusion rate must not exceed 5mg/min so total infusion time must be extended for doses >600mg).

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 at a reduced infusion rate 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
- 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.

H₂ antagonist or proton-pump inhibitor if required.

Loperamide if required.

Doxycycline 100mg OD, 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 irritant (Group 3).
Fluorouracil is an inflamatant (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.

DPYD status must be available prior to starting fluorouracil treatment as per local practice.

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	$\geq 1.5 \times 10^9/L$
Platelets	$\geq 100 \times 10^9/L$
AST/ALT	$\leq 1.5 \times ULN$
Alkaline Phosphatase	$\leq 2.5 \times ULN$
Creatinine Clearance (CrCl)	$> 30\text{mL}/\text{min}$
Magnesium	$\geq 0.7 \text{ mmol}/L$ (see below for replacement)

Dose modifications

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

- **Haematological toxicity**

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

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 during periods of myelosuppression, discuss with consultant.

• **Renal impairment**

Carboplatin:

CrCl (mL/min)	Carboplatin dose
> 30	100%
20-30	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.

Fluorouracil: Consider dose reduction in severe renal impairment (CrCl<30mL/min) – discuss with consultant

Cetuximab: There is little experience of administering cetuximab in patients with renal impairment but no need for dose adjustment is expected. Discuss with consultant if CrCl <30ml/min.

• **Hepatic impairment**

Fluorouracil:

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 on subsequent cycles if no toxicity.

Carboplatin: 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.

Cetuximab: There is little experience of administering cetuximab in patients with hepatic impairment but no need for dose adjustment is expected If AST/ALT > 3 x ULN or bilirubin > ULN discuss with consultant.

• **Other toxicities**

Toxicity	Definition	Dose adjustment	
		Fluorouracil	Carboplatin
Diarrhoea*	Grade 1: Manage symptomatically with loperamide +/- codeine phosphate	100%	100%
	Grade 2: 2 nd occurrence	80%	100%
	Grade 3: 1 st occurrence	80%	100%
	Grade 3: 2 nd occurrence	50%	80%
	Grade 4: 1 st occurrence	Discontinue treatment	
Stomatitis/Mucositis*	Grade 1: Manage symptomatically with mouthwashes	100%	100%
	Grade 2: 2 nd occurrence	80%	100%
	Grade 3: 1 st occurrence	80%	100%
	Grade 3: 2 nd occurrence	50%	80%
	Grade 3: 3 rd occurrence	Discontinue treatment	
	Grade 4: 1 st 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 or as per local policy	
	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 \geq grade 2 stomatitis or diarrhoea, fluorouracil must not be given. Treatment must be deferred one week until toxicity has resolved to \leq 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 \geq grade 2 consider increasing doxycycline to 100mg BD until improves
- If \geq grade 3 suspend until resolution \leq grade 2 and increase doxycycline to 100mg BD to continue throughout treatment (if \geq 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 (\geq grade 3 acneiform rash). Treatment may only be resumed if the reaction has resolved to grade 2, according to the dosing table below:

\geq Grade 3 acneiform rash	Cetuximab weekly dose after resolution to \leq grade 2
1 st occurrence	100% previous dose
2 nd occurrence	Reduce from 250 mg/m ² to 200 mg/m ²
3 rd occurrence	Reduce from 200 mg/m ² to 150 mg/m ²
4 th occurrence	Discontinue permanently

If the skin reaction does not resolve to \leq 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
Onychia

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 can result in severe toxicity secondary to reduced fluorouracil metabolism (this can present as severe diarrhoea and/or severe stomatitis early in the first cycle). Check for DYPD mutations prior to prescribing 5FU and dose reduce according to result. Go ahead prior to testing should only be authorised by managing consultant and after discussion of risks with patient.

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 or carboplatin.

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 (TA473) accessed 24 November 2022 via www.nice.org.uk
- Summary of Product Characteristics Carboplatin (Hospira) accessed 24 November 2022 via www.medicines.org.uk
- Summary of Product Characteristics Fluorouracil (Hospira) accessed 24 November 2022 via www.medicines.org.uk
- Summary of Product Characteristics Cetuximab (Merck Serono) accessed 24 November 2022 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

Written/reviewed by: Dr E de Winton (Consultant Oncologist, RUH Bath NHS Trust), Dr M Beasley (Consultant Oncologist, UHBW NHS Trust)

Checked by: Kate Gregory (Lead Pharmacist for SACT Protocols, SWAG Cancer Alliance)

Authorised by: Dr J Braybrooke (Consultant Oncologist, UHBW NHS Trust and SWAG Cancer Alliance)

Date: November 2022
