Cetuximab, Cisplatin and Fluorouracil (head and neck)

Indication
First line treatment of recurrent or metastatic head and neck squamous cell cancer.

ICD-10 codes
Codes prefixed with C00-C13

Regimen details

Day	Drug	Dose	Route
1 (loading dose)	Cetuximab	400mg/m^2	IV infusion
then weekly maintenance dose (ie days, 8, 15 and day 1, 8 and 15 of future cycles)	Cetuximab	250mg/m2	IV infusion
1	Cisplatin	80mg/m^2	IV infusion
1-4*	Fluorouracil	1000mg/m^2/day	Continuous IV infusion

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

Cycle frequency
21 days

Number of cycles
Up to 6 cycles.
Maintenance cetuximab – 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

Cisplatin is administered in 500mL sodium chloride 0.9% over 1 hour following the pre and post hydration protocol below.

Infusion Fluid & Additives	Volume	Infusion Time
Sodium Chloride 0.9%	1000mL	1 hour
Mannitol 20% **OR** Mannitol 10%	200mL 400mL	30 minutes 30 minutes
Ensure urine output > 100mL / hour prior to giving cisplatin. Give a single dose of furosemide 20mg iv if necessary.		
Cisplatin	500mL	1 hour
Sodium Chloride 0.9% + 2g $MgSO_4$ + 20mmol KCl	1000mL	2 hours
TOTAL	**2700mL or 2900mL**	**4 hours 30 minutes**

Patients with low magnesium levels (<0.7 mmol/L) should have an additional 2g magnesium sulphate added to the pre-hydration bag.

An accurate fluid balance record must be kept.

All patients must be advised to drink at least 2 litres of fluid over the following 24 hours.

Fluorouracil is administered by continuous infusion via ambulatory pump over 4 days 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

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

Emetogenicity

This regimen has a high emetogenic potential.

Additional supportive medication

Mouthwashes as per local policy.
H_2 antagonist or proton-pump inhibitor if required.
Loperamide if required.
See below for guidelines for 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. For example magnesium glycerophosphate [Note: unlicensed product] 24 mmol Mg^{2+} per day in divided doses or as per local magnesium replacement guidelines.

Extravasation

Cetuximab is neutral (Group 1)
Fluorouracil is an inflammatant (Group 2).
Cisplatin is an exfoliant (Group 4).

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
Calcium	14 days

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)	> 60mL/min
Magnesium	≥ 0.7 mmol/L

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 cisplatin and fluorouracil to 80% for all future cycles.
If grade 4 haematological toxicity occurs discontinue chemotherapy

Cetuximab may be continued, discuss with consultant.

- ### Renal impairment

CrCl (mL/min)	**Cisplatin Dose**
> 60	100%
51-60	75%
40-50	50% or switch to carboplatin AUC5
<40	Contraindicated

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

*Fluorouracil can be increased if no toxicity.
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	**Cisplatin**
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 3 3rd occurrence	Discontinue treatment	
	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	

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 follow the guidelines below:
- Ensure regular use of moisturiser
- Start doxycycline 100mg OD to continue throughout treatment (increase to BD if ≥ grade 3 and if no response consider switching to erythromycin 500mg QDS)
- Oral antihistamine for pruritis

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
Neutropenic sepsis
S.aureus super-infection
Infusion related toxicity
Cardiac toxicity
Secondary malignancy
Teratogenicity
Renal impairment
Neurotoxicity

- **Frequently occurring side effects**

Nausea and vomiting
Diarrhoea or constipation
Stomatitis and mucositis
Skin reactions
Headache
Dyspnoea
Conjunctivitis
Electrolyte imbalances particularly hypomagnaesaemia
Peripheral neuropathy
Tinnitus/ototoxicity
Palmar-plantar erythema
Alopecia (mild)

- **Other side effects**

Electrolyte imbalances
Cutaneous effects
Loss of appetite, taste alterations (metallic)
Fatigue
Sore eyes and runny nose
Fluid retention
Rare vascular toxicity including coronary vasospasm
Allergic reactions

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.
Antibiotics: The renal toxicity of cisplatin is potentiated by aminoglycoside antibacterials (e.g. gentamicin) and amphotericin. Aminoglycosides should be avoided. If aminoglycosides are prescribed, close monitoring of renal function and serum antibiotic levels is required.
Avoid all nephrotoxic drugs where possible

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). Do not use in patients with known DPD deficiency.

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.

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

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

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

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