Cetuximab, Cisplatin and Fluorouracil

Indication

Treatment of recurrent or metastatic squamous cell carcinoma of the head and neck where the cancer started in the oral cavity. PS0-1

NICE TA473

ICD-10 codes

Codes prefixed with C00-C13

Regimen details

Cycle 1:

Day	Drug	Dose	Route
1 (loading dose)	Cetuximab	400mg/m^2	IV infusion
8, 15	Cetuximab	250mg/m^2	IV infusion
1	Cisplatin	100mg/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

Subsequent cycles:

Day	Drug	Dose	Route
1, 8 and 15	Cetuximab	250mg/m^2	IV infusion
1	Cisplatin	100mg/m^2	IV infusion
1-4*	Fluorouracil	1000mg/m^2/day	Continuous IV infusion

Cetuximab maintenance - two-weekly regimen*

Cycle	Day	Drug	Dose	Route
Cycle 1 only	1	Cetuximab	400mg/m^2	IV infusion
	8	Cetuximab	250mg/m^2	IV infusion
Cycle 2 onwards	1	Cetuximab	500mg/m^2	IV infusion

* Note: this dosing regimen is unlicensed.

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 1000mL 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
Sodium Chloride 0.9%	500mL	30 minutes
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	1000mL	2 hours
Mannitol 20% **OR** Mannitol 10%	200mL 400mL	30 minutes 30 minutes
Sodium Chloride 0.9% + 2g $MgSO_4$ + 20mmol KCl	1000mL	2 hours
TOTAL	**3700mL or 3900mL**	**5 hours 50 minutes**

Patients with low magnesium levels may have an additional 2g magnesium sulphate added to the pre-hydration regimen.

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 (or alternative H_2 antagonist)
- Dexamethasone 8mg IV
- Paracetamol 500mg-1g PO

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

Emetogenicity
This regimen has high emetogenic 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)
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
Bilirubin	≤ 1.5 x ULN
AST/ALT	≤ 1.5 x ULN
Alkaline Phosphatase	≤ 2.5 x ULN
Creatinine Clearance (CrCl)	> 60mL/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 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	
Hypomagnesaemia	<0.4mmol/l or 0.4-0.6 mmol/l (symptomatic)	IV Magnesium Sulphate 4g 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 and 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 for 1 week (then reducing by 5 mg / 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%
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

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 as a result of polymorphism variants in the DPYD gene can result in severe toxicity secondary to reduced fluorouracil metabolism. This is common; affecting 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. **It is recommended 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.

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

- National Institute for Clinical Excellence (TA 473) accessed 24 October 2019 via www.nice.org.uk
- Summary of Product Characteristics Cisplatin (Hospira) accessed 24 October 2019 via www.medicines.org.uk
- Summary of Product Characteristics Fluorouracil (Hospira) accessed 24 October 2019 via www.medicines.org.uk
- Summary of Product Characteristics Cetuximab (Merck Serono) accessed 24 October 2019 via www.medicines.org.uk
- Segaert, S et al; Ann Oncol 2005; 16: 1425 – 1433
- Vermorken, JB et al; NEJM 2008; 359 (11): 1116 - 1127

Written/reviewed by: De E de Winton (Consultant Oncologist, RUH Bath NHS Trust)

Checked by: Sarah Murdoch (Senior Oncology Pharmacist, SW Clinical Network)

Authorised by: Dr J Braybrooke (Consultant Oncologist, SW Clinical Network)

Date: November 2019