Cisplatin and Fluorouracil (Head & Neck)

Indication

Neo-adjuvant treatment prior to chemo-radiotherapy for locally advanced squamous cell carcinomas of the head and neck.

Performance Status 0-1

ICD-10 codes

Codes prefixed with C00-13

Regimen details

Day	Drug	Dose	Route
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

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

Cycle frequency

21 days

Number of cycles

2 - 3 cycles

Administration

Cisplatin is administered in 1000mL sodium chloride 0.9% over 2 hours 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**	**6 hours 30 minutes**

Patients with magnesium levels below the lower limit of normal should 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 have at least 3 litres of fluid daily over the following week orally or via gastrostomy.

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

Nil

Emetogenicity

This regimen has a high and delayed emetogenic potential. An NK1 inhibitor as well as extending dexamethasone and 5HT3 antagonist for at least 5 days post chemotherapy is recommended.

Additional supportive medication

Mouthwashes as per local policy.
Proton-pump inhibitor if required.
Loperamide if required.
Oral magnesium supplementation between cycles in addition to the intravenous magnesium administered at the time of chemotherapy if required (see below).

Extravasation

Cisplatin is an exfoliant (Group 4).
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

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
Haemoglobin (Hb)	≥100g/L
Neutrophils	≥ 1.5 x 10^9/L
Platelets	≥ 100 x 10^9/L
Bilirubin	≤ ULN
AST/ALT	≤ 1.5 x ULN
Alkaline Phosphatase	≤ 2.5 x ULN
Creatinine Clearance (CrCl)*	> 60mL/min
Magnesium	≥ 0.6 mmol/L

*Formal measurement of renal function should be considered if calculated CrCl by Cockroft Gault is borderline or at extremes of BSA prior to first dose.

Dose modifications

- **Haematological toxicity**

Neutrophils (x 10^9/L)		**Platelets** (x 10^9/L)	**Cisplatin dose**
≥1.5	and	≥100	100%
1.0-1.4	or	50-99	Delay 1 week (continue radiotherapy) Consider GCSF if neutropenic. If FBC recovers continue 100% dose.
<1.0	or	<50	Delay 1 week (continue radiotherapy) Give GCSF if neutropenic. If FBC recovers continue with 100% of dose*

*If delayed on two occasions for grade 3 haematological toxicity reduce cisplatin and fluorouracil to 80% for all future cycles. If grade 4 haematological toxicity discontinue treatment.

If Hb <80 g/L arrange 1-2 unit transfusion

- **Renal impairment**

Cisplatin:

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

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

- **Hepatic impairment**

Fluorouracil:

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

*Fluorouracil can be increased if no toxicity.
If bilirubin > ULN discuss with consultant.

Cisplatin: No dose modification required

- **Other toxicities**

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

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 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	Discuss with consultant about discontinuing treatment	
	Grade 4: 1st occurrence	Discuss with consultant about discontinuing treatment	
Hypomagnesaemia	<0.4mmol/L (symptomatic)	IV Magnesium Sulphate 2-4g as per local policy	
	<0.4mmol/L (asymptomatic)	Oral Magnesium salts 8mmol 2-3 x daily or as per local policy	
	0.4 – 0.6 mmol/L	Supplementation if symptomatic or ongoing risk orally 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.

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

- **Serious side effects**

Myelosuppression
Cardiac toxicity
Secondary malignancy
Teratogenicity
Renal impairment
Neurotoxicity

- **Frequently occurring side effects**

Nausea and vomiting
Diarrhoea or constipation
Myelosuppression
Stomatitis and mucositis
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.
Sorivudine: Inhibits dihydropyrimidine dehydrogenase – use with caution.
Phenytoin: Increased phenytoin plasma concentrations have been reported during concomitant use of phenytoin with fluorouracil.
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). Check for DPYD 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 cisplatin or mannitol.

References

- Posner MR, Hershock DM, Blajman CR, Michiewicz E; Winquist E, Gorbounova V et al. Cisplatin and Fluorouracil Alone or with Docetaxel in head and Neck Cancer. N Engl J Med. 2007;257:1705-15
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- Allwood M, Stanley A, Wright P, editors. The cytotoxics handbook. 4th ed. Radcliffe Medical Press. 2002.

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Date: November 2022