Cisplatin and Fluorouracil (palliative)

Indication

Palliative chemotherapy for recurrent or metastatic head and neck squamous cell cancer where combination treatment with cetuximab is not indicated. PS0-1

ICD-10 codes

Codes prefixed with C00-C13

Regimen details

Day	Drug	Dose	Route
1	Cisplatin	75mg/m^2	IV infusion
1-4*	Fluorouracil	750mg/m^2/day	Continuous IV infusion

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

Cycle frequency

21 days

Number of cycles

Palliative - up to 6 cycles

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 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
Nil

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.
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
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

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	≤ ULN
AST/ALT	≤ 1.5 x ULN
Alkaline Phosphatase	≤ 2.5 x ULN
Creatinine Clearance (CrCl)	> 60mL/min
Magnesium	≥ 0.6 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 discontinue treatment.

- **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

- **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	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.
No hepatic function dose modifications required for cisplatin.
If 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 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 (symptomatic)	IV Magnesium Sulphate 4g 1000mL sodium chloride 0.9% over 4 hours	
	<0.4mmol/l (asymptomatic)	Oral Magnesium salts 8mmol BD	
	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.
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). Avoid 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.

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
- Summary of Product Characteristics Cisplatin (Hospira) accessed 6 December 2017 via www.medicines.org.uk
- Summary of Product Characteristics Fluorouracil (Hospira) accessed 6 December 2017 via www.medicines.org.uk
- Allwood M, Stanley A, Wright P, editors. The cytotoxics handbook. 4th ed. Radcliffe Medical Press. 2002.

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