TPF - Docetaxel, Cisplatin and Fluorouracil (head and neck)

Indication
Neo-adjuvant treatment prior to definitive chemo-radiotherapy for locally advanced head and neck squamous cell cancer

ICD-10 codes
Codes prefixed with C00-C13

Regimen details

Day	Drug	Dose	Route
1	Docetaxel	75mg/m^2	IV infusion
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
Maximum of 3 cycles

Administration
Docetaxel is administered as an IV infusion in 250mL or 500mL (concentration dependent) PVC free sodium chloride 0.9% over 60 minutes.

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

Dexamethasone 8 mg BD (morning and lunchtime) for 3 days starting 24 hours prior to chemotherapy. (Note: Patients must receive 3 doses of dexamethasone prior to treatment)

Emetogenicity

This regimen has a high emetogenic potential

Additional supportive medication

GCSF (as per local policy) as primary prophylaxis against neutropenic infection.
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 and docetaxel are exfoliants (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	≥ 0.7 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 docetaxel, fluorouracil and cisplatin to 80% for all future cycles.
If grade 4 haematological toxicity stop chemotherapy.

- **Renal impairment**

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

Reduce fluorouracil dose only in severe renal impairment – discuss with consultant
No dose modification for renal impairment required for docetaxel

- **Hepatic impairment**

AST +/or ALT		**Alkaline Phosphatase**	**Docetaxel Dose**	**Fluorouracil dose**
≤ 1.5 x ULN	and	≤ 2.5 x ULN	100%	100%
>1.5 - ≤ 3.5 x ULN	and/or	> 2.5 -≤ 6 x ULN	75%	Start at 80%*
> 3.5 x ULN	and/or	> 6 x ULN	Delay and discuss with consultant.	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	**Docetaxel**	**Cisplatin**
Diarrhoea	Grade 1: Manage symptomatically with loperamide +/or codeine phosphate	100%	100%	100%
	Grade 2	80%	100%	100%
	Grade 3	50%	80%	80%
	Grade 3: 2nd occurrence	Discontinue treatment		
	Grade 4	Discontinue treatment		
Stomatitis/Mucositis	Grade 1: Manage symptomatically with mouthwashes	100%	100%	100%
	Grade 2	80%	100%	100%
	Grade 3:	50%	80%	80%
	Grade 3: 2nd occurrence	Discontinue treatment		
	Grade 4:	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.

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
Myalgia/Arthralgia
Palmar-plantar erythema
Alopecia

- **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

Enzyme inducers/inhibitors: *in vitro* studies suggest that CYP3A inhibitors (such as ketoconazole and erythromycin) will raise docetaxel levels, whereas CYP3A inducers (such as rifampicin and barbiturates) will reduce docetaxel levels. This has been seen for ketoconazole
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 – switch patients to low molecular weight heparin during treatment – elevations in INR
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
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