Systemic Anti Cancer Treatment Protocol

TPF
Head and Neck

PROTOCOL REF: MPHAHANTPF
(Version No: 1.1)

Approved for use in:

Head and neck cancer locally advanced disease – Neoadjuvant chemotherapy for up to 3 cycles

Creatinine clearance at baseline > 50mL/min

Dosage:

Drug	Dose	Route	Frequency
Docetaxel	75mg/m^2	IV infusion	Day 1
Cisplatin	75mg/m^2	IV infusion	Day 1
Fluorouracil	750mg/m^2/day	IV infusion over 24 hours	Days 1 to 4 of a 21 day cycle

Repeat at 21 day intervals for up to 3 cycles prior to radiotherapy

Supportive Treatments:

Premedication of dexamethasone 8 mg twice daily for 3 days starting 1 day prior to docetaxel administration
Fosaprepitant 150mg IV 30minutes before chemotherapy
Ciprofloxacin 500mg twice daily for seven days from day 5
Filgrastim subcutaneously once daily for 7 days starting on day 5
(300micrograms for patients below 70kg, 480micrograms for patients above 70kg)
Domperidone tablets 10mg three times daily when required

Extravasation risk:

Docetaxel:

Cisplatin: Injection site reactions may occur during the administration of cisplatin.

Fluorouracil: refer to local guidelines for management extravasation

Administration:

- Review patient's fluid intake over the previous 24 hours
- Review common toxicity criteria and performance status
- Calculate creatinine clearance using Cockcroft and Gault equation (see investigation section)
- Weigh the patient prior to commencing intravenous fluids
- Commence strict fluid balance (input and output)

Outpatient regimen

Day	Drug	Dose	Route	Diluent and rate
Pre med	Dexamethasone starting 1 day prior to docetaxel administration	8 mg twice daily for 3 days	PO	
1	Fosaprepitant	150mg	IV	100mL sodium chloride 0.9% over 30 minutes
	Ondansetron tablets 30mins before chemotherapy	16mg	PO	
	Docetaxel	**75mg/m^2**	**IV**	250mL sodium chloride 0.9% over 60 minutes
	Furosemide tablets	20mg	PO	
	Sodium chloride 0.9% 1000mL with 20mmol potassium chloride		**IV over 90 minutes**	
	Measure urine output volume and record If urine output averages 100mL/hour over previous 3 hours then proceed with cisplatin infusion If urine output is less than 100mL/hour the patient should be assessed and further 500mL sodium chloride 0.9% given IV over 30 minutes If urine output still not adequate contact the head and neck team			
	Cisplatin	**75mg/m^2**	**IV**	1000mL sodium chloride 0.9% over 90 minutes
	Sodium chloride 0.9% 1000mL with 20mmol potassium chloride		**IV over 90 minutes**	
	Fluorouracil In infusion device (Baxter LV2 pump)	**3000mg/m^2** **(750mg/m^2/day for 4 days)**	**IV**	195mL sodium chloride 0.9% over 4 days (96 hours)

If PICC line placement is not possible then the inpatient regimen can be used as an alternative.

Inpatient regimen

Day	Drug	Dose	Route	Diluent and rate
Pre med	Dexamethasone starting 1 day prior to docetaxel administration	8 mg twice daily for 3 days	PO	
1	Fosaprepitant	150mg	IV	100mL sodium chloride 0.9% over 30 minutes
	Ondansetron tablets 30mins before chemotherapy	16mg	PO	
	Docetaxel	**75mg/m^2**	**IV**	250mL sodium chloride 0.9% over 60 minutes
	Furosemide tablets	20mg	PO	
	Sodium Chloride 0.9% 1000mL (+ 20mmol Potassium Chloride)		**IV over 90 minutes**	
	Measure urine output volume and record If urine output averages 100mL/hour over previous 3 hours then proceed with cisplatin infusion If urine output is less than 100mL/hour the patient should be assessed and further 500mL sodium chloride 0.9% given IV over 30 minutes If urine output still not adequate contact the head and neck team			
	Cisplatin	**75mg/m^2**	**IV**	1000mL sodium chloride 0.9% over 90 minutes
	Sodium Chloride 0.9% 1000mL (+ 20mmol Potassium Chloride)		**IV over 90 minutes**	
	Fluorouracil	**750mg/m^2**	**IV**	1000mL sodium chloride 0.9% over 24hours
2	**Fluorouracil**	**750mg/m^2**	**IV**	1000mL sodium chloride 0.9% over 24hours
3	**Fluorouracil**	**750mg/m^2**	**IV**	1000mL sodium chloride 0.9% over 24hours
4	**Fluorouracil**	**750mg/m^2**	**IV**	1000mL sodium chloride 0.9% over 24hours

At the end of IV fluids:

- **Weigh the patient and review fluid balance chart**
- **If there is a positive balance of 1.5L or 1.5kg in weight gained then consider furosemide 20mg orally and review output after 30 minutes. Any concerns then discuss with medical team prior to discharging the patient.**

Ensure good oral (or via PEG) fluid intake

- **Confirm patient understanding of the importance of fluid intake**
- **Patient should ensure they have 2 litres of fluid in the 24 hours following chemotherapy**

Main Toxicities:

Immunosuppression (neutropenia, thrombocytopenia, anaemia), stomatitis, diarrhoea, nausea, vomiting, constipation, neuropathy, alopecia, hypersensitivity reactions, infertility

Docetaxel	
Respiratory disorders	Acute respiratory distress syndrome, interstitial pneumonia/pneumonitis, interstitial lung disease, pulmonary fibrosis and respiratory failure have been reported and may be associated with fatal outcome. If new or worsening pulmonary symptoms develop, patients should be closely monitored, promptly investigated.
Skin and subcutaneous tissue disorders	Localised rash including severe hand and foot syndrome. Less frequently, severe symptoms such as eruptions followed by desquamation. Severe nail disorders: Hypo- or hyperpigmentation and sometimes pain and separation of the nail from the nail bed.
Other/General disorders and administration site conditions	<u>Eye disorders</u> Cystoid macular oedema (CMO) has been reported. Patients with impaired vision should undergo a prompt and complete ophthalmologic examination. <u>Fluid retention</u> Includes events such as peripheral oedema and less frequently pleural effusion, pericardial effusion, ascites and weight gain. Fluid retention is cumulative in incidence and severity.

Cisplatin	
Nephrotoxicity	Urine output of 100 mL/hour or greater will help minimise cisplatin nephrotoxicity
Ototoxicity	Observed in up to 31% of patients can be unilateral or bilateral and tends to become more frequent and severe with repeated doses; It is unclear whether ototoxicity is reversible

Fluorouracil	
Ocular	Nystagmus, watery eyes from increased production of Tears, gritty, red, sore eyes and blurred vision
Hepatobiliary disorders	Liver cell damage, liver necrosis, biliary sclerosis, cholecystitis
Dermatological	Palmar – plantar syndrome (hand-foot syndrome), on the palms of the hands and soles of the feet Hyperpigmentation of the skin Brittle, chipped and ridged nails –blue tinge or darkening or the nails, flaking of the nails, or pain and thickening of the nail bed. Sensitivity of the skin to sunlight
Cardiovascular	**Cardiac disorders** Common - Angina, Ischemic ECG abnormalities Uncommon - Arrhythmia, myocardial infarction, myocardial ischaemia myocarditis, dilative cardiomyopathy, and cardiac shock. Very rare - Cardiac arrest, sudden cardiac death Cardio toxic adverse events mostly occur during or within hours following the first treatment cycle. There is an increased risk of cardio toxicity in patients with previous coronary heart disease or cardiomyopathy **Vascular disorders** Cerebral, intestinal and peripheral ischemia

Cockcroft and Gault formula

Male patients $\frac{1.23 \times (140 - \text{age}) \times \text{weight (kg)}}{\text{Serum Creatinine (micromol/L)}}$

Female patients $\frac{1.04 \times (140 - \text{age}) \times \text{weight (kg)}}{\text{Serum Creatinine (micromol/L)}}$

Investigations:

	Pre	C1	C2	C3	Comments
Medical Assessment	X			X	at end of treatment
Nursing Assessment		X	X	X	Every cycle
FBC	X	X	X	X	Every cycle
U&E & LFTs	X	X	X	X	Every cycle
CrCl (Cockcroft and Gault)	X	X	X	X	
CT scan	X				As clinically indicated
Informed Consent	X				
Blood glucose	X				Repeat if clinically indicated
Blood pressure measurement	X	X	X	X	
PS recorded	X	X	X	X	Every cycle
Toxicities documented	X	X	X	X	Every cycle
Weight recorded	X	X	X	X	Every cycle

Dose Modifications and Toxicity Management:

Consider dose modifications for intolerable grade 2 or any grade 3 toxicities

Recommended dose reduction for toxicity management	Docetaxel	Cisplatin	Fluorouracil
First dose reduction	60mg/m^2	60mg/m^2	600mg/m^2
Second dose reduction	40mg/m^2	40mg/m^2	500mg/m^2

Haematological Toxicity:

Proceed on day 1 if-

ANC ≥ 1.0 x 10^9/L	Plt ≥ 100 x 10^9/L

Delay 1 week and consider dose reduction on day 1 if-

ANC ≤ 0.9 x 10^9/L	Plt ≤ 99 x 10^9/L

These nhaematological guidelines assume that patients are well with good performance status, that other acute toxicities have resolved and the patient has not had a previous episode of neutropenic sepsis.

Hepatic impairment:

Docetaxel
If bilirubin >22µmol/L and/or ALT/AST > 3.5 x ULN with ALP > 6 x ULN, docetaxel should not be used unless strictly indicated.

Fluorouracil			
Bilirubin /µmol/L		**AST/ALT /units**	**Dose**
<85		<180	No dose modification
>85	or	>180	Contra indicated

Cisplatin – no dose reduction necessary

Renal impairment:

Cisplatin: GFR (mL/min)	**Dose**
Above 60	75mg/m^2 (100% dose)
50 to 59	60mg/m^2 (75% dose)
Below 50	Refer patient to treating consultant oncologist for treatment review

Fluorouracil
Dose adjustments of fluorouracil not required until clearance falls below 30mL/min

If creatinine clearance falls below 50mL/min, discuss with consultant as combination therapy may no longer be appropriate

References:

Posner et al
Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer
NEJM 2007 357(17): 1705-1715

Cisplatin 1 mg/ml Sterile Concentrate: Summary of Product Characteristics Hospira UK Ltd Warwickshire.06/09/1996. Available from: www.medicines.org.uk/emc/medicine. Last updated 30/04/2013.

Fluorouracil 50 mg/ml Solution for Injection or Infusion: Summary of Product Characteristics, Hospira, Warwickshire. 19/07/2004. Available from: www.medicines.org.uk/emc/medicine. Last updated 24/07/14.

Docetaxel Accord 80mg/4ml concentrate for solution infusion, Summary of Product Characteristics. Accord Healthcare Limited Middlesex. 22/05/2012. Available from: www.medicines.org.uk/emc/medicine. Last updated 10/07/2014.

Dosage Adjustment for Cytotoxics in Hepatic Impairment. January 2009 UCLH (Version 3 - updated January 2009)

Dosage Adjustment for Cytotoxics in Renal Impairment. January 2009 UCLH (Version 3 - updated January 2009)