Systemic Anti-Cancer Treatment Protocol

CISPLATIN AND FLUOROURACIL
Head and Neck Cancer

PROCEDURE REF: MPHACISFLU
(Version No: 1.2)

Approved for use in:

Head and neck cancer locally advanced disease – given as 2 cycles prior to radiotherapy.

Metastatic head and neck cancer – up to 6 cycles as palliative treatment

Creatinine clearance at baseline > 50mL/min

Dosage:

Drug	Dose	Route	Frequency
Cisplatin	**80mg/m^2**	IV infusion	Day 1 only of a 21 day cycle
Fluorouracil	**1000mg/m^2/day**	IV infusion over 24hours	Day 1 to 4 of a 21 day cycle

Repeat at 21 day interval for up to 6 cycles for metastatic disease

Repeat at 21 to 28 day intervals for 2 cycles if administering prior to radiotherapy

Supportive Treatments:

Aprepitant 125mg to be taken on day 1, an hour before chemotherapy and 80mg to be taken as a single dose on day 2 and day 3

Dexamethasone tablets, 4mg twice daily for 3 days

Domperidone 10mg tablets, to be taken up to three times a day when required

Extravasation risk:

Cisplatin: Injection site reactions may occur during the administration of cisplatin. Given the possibility of extravasation, it is recommended to closely monitor the infusion site for possible infiltration during drug administration. A specific treatment for extravasation reactions is unknown at this time

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)

Inpatient regimen

Day	Drug	Dose	Route	Diluent and rate
1	**Aprepitant** 1 hour before chemotherapy (80mg to be taken as a single dose on day 2 and day 3)	**125mg**	**PO**	
	Ondansetron tablets 30mins before chemotherapy	**24mg**	**PO**	
	Dexamethasone tablets 30mins before chemotherapy	**12mg**	**PO**	
	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	**80mg/m^2**	**IV**	Sodium Chloride 0.9% 1000mL over 90 minutes

	Sodium Chloride 0.9% 1000mL (+ 20mmol Potassium Chloride)		**IV over 90 minutes**	
	Fluorouracil	**1000mg/m^2**	**IV**	Sodium Chloride 0.9% 1000mL over 24hours
2	**Fluorouracil**	**1000mg/m^2**	**IV**	Sodium Chloride 0.9% 1000mL over 24hours
3	**Fluorouracil**	**1000mg/m^2**	**IV**	Sodium Chloride 0.9% 1000mL over 24hours
4	**Fluorouracil**	**1000mg/m^2**	**IV**	Sodium Chloride 0.9% 1000mL over 24hours

Outpatient regimen

Day	Drug	Dose	Route	Diluent and rate
1	**Aprepitant** 1 hour before chemotherapy (80mg to be taken as a single dose on day 2 and day 3)	**125mg**	**PO**	
	Ondansetron tablets 30mins before chemotherapy	**24mg**	**PO**	
	Dexamethasone tablets 30mins before chemotherapy	**12mg**	**PO**	
	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	**80mg/m^2**	**IV**	Sodium Chloride 0.9% 1000mL over 90 minutes
	Sodium Chloride 0.9% 1000mL (+ 20mmol Potassium Chloride)		**IV over 90 minutes**	
	Fluorouracil (1000mg/m^2/day for 4 days)	**4000mg/m^2**	**IV**	Sodium Chloride 0.9% 195mL over 4 days (96 hours)

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:

Haematological: Myelosuppression: neutropenia, thrombocytopenia, anaemia

Gastrointestinal: Anorexia, nausea, vomiting and diarrhoea, mucositis (stomatitis, oesophagitis, pharyngitis, proctitis), bitter or metallic taste disturbance

Cisplatin	
Nephrotoxicity	Urine output of 100 mL/hour or greater will help minimise cisplatin nephrotoxicity
Neuropathies	May be irreversible and may manifest by paresthesia, loss of muscle reflex and a sensation of vibrations. A neurologic examination must be carried out at regular intervals.
Ototoxicity	Observed in up to 31% of patients can be unilateral or bilateral and tends to become more frequent and severe with repeated doses; consider audiometry and referral to ENT specialist
Additional side effects	Loss of fertility Anaphylactic reactions
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 Alopecia (hair may thin unlikely to cause total hair loss) 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	Common - Angina, Ischemic ECG abnormalities Uncommon - Arrhythmia, myocardial infarction, myocardial ischaemia myocarditis, dilative cardiomyopathy, and cardiac shock. Very rare - Cardiac arrest, sudden cardiac death **Vascular disorders** Cerebral, intestinal and peripheral ischemia

Investigations and treatment plan:

	Pre	Cycle 1	Cycle 2	Cycle 3	Ongoing
Medical Assessment	X			X	Weekly review in floor clinic if undergoing radiotherapy. At end of treatment
Nursing Assessment		X	X	X	Every cycle
FBC	X		X	X	Every cycle
U&E & LFT	X		X	X	Every cycle
Calculate CrCl	X	X	X	X	Every cycle
Dihydropyrimidine dehydrogenase (DPD) deficiency test	X				This test is normally only required if a patient has not had capecitabine, or fluorouracil in the past. However a consultant may still request this test if capecitabine or fluorouracil was not tolerated previously. The result must be available before administration of chemotherapy unless clear documentation from the consultant is available to the contrary. Treatment with capecitabine and fluorouracil is contraindicated in patients with known complete DPD deficiency.
CT scan	X				As clinically indicated

Informed Consent	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

Cockcroft and Gault formula

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

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

Dose Modifications and Toxicity Management:

Cisplatin	**Recommended dose reduction for toxicity management**
First dose reduction	60mg/m^2
Second dose reduction	40mg/m^2

Fluorouracil	**Recommended dose reduction for toxicity management**
First dose reduction	750mg/m^2/day
Second dose reduction	500mg/m^2/day

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

Hepatic impairment:

Fluorouracil			
Bilirubin µmol/L		**AST/ALT units**	**Dose**
<85		<180	No dose modification
>85	or	>180	Contra indicated
Although 50 to 80% of fluorouracil is metabolised by the hepatic route, the clinical significance is unclear. Some studies of plasma and tissue concentration of the drug and derivatives in patients with hepatocellular carcinoma and liver cirrhosis or liver metastases detected no change in drug disposition relating to liver dysfunction, indicating no dose reduction is required. However, a dose reduction of the initial dose is advised of 1/3 to ½ in hepatic impairment, which may be increase if no toxicity is observed.			

Cisplatin: No dose reduction necessary.

Renal impairment:

Cisplatin: GFR (mL/min)	Dose
> 60	80mg/m^2 (100% dose)
45-59	60mg/m^2 (75% dose)
< 45	Consider carboplatin

If serum creatinine has increased by 50% between cycles then 20% dose reduction is required at next cycle.

Fluorouracil
Fluorouracil is predominantly eliminated by liver 60-80% is excreted as respiratory CO_2, 2-3% by biliary system. Following a single IV dose, approximately 15% of the dose is excreted unchanged in the urine. Consider dose reduction in severe renal impairment only in patients with creatinine clearance below 30m/min.

References:

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 https://www.medicines.org.uk/emc Last updated 24/07/14.

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

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

Forastiere AA et al
Randomised comparison of cisplatin plus fluorouracil and carboplatin plus fluorouracil versus methotrexate in advanced squamous cell carcinoma of the head and neck: a SWOG study
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