Systemic Anti Cancer Treatment Protocol

CISPLATIN AND FLUOROURACIL
Penile Cancer

PROCTOCOL REF: MPHACISFL
(Version No: 1.1)

Approved for use in:

Advanced penile cancer

Creatinine clearance at baseline >50ml/min

Dosage:

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

Starting dose may be adjusted to cisplatin 60mg/m^2 and fluorouracil 3000mg/m^2 over 96 hours

Repeat at 21 day intervals for 4 to 6 cycles.

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.

Flourouracil: refer to local guidelines for management extravasation

Cockroft and Gault formula

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

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

Administration:

- Review patient's fluid intake over the previous 24 hours
- Review common toxicity criteria and performance status
- Calculate creatinine clearance using Cockroft and Gault equation
- 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** 60 minutes before chemotherapy	**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 With 20mmol Potassium Chloride		**IV infusion 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 oncologist**			
	Cisplatin	**80mg/m^2**	**IV**	Sodium Chloride 0.9% 1000mL over 90 minutes
	Sodium Chloride 0.9% 1000mL With 20mmol Potassium Chloride		**IV infusion over 90 minutes**	
	Fluorouracil	**1000mg/m^2**	**IV**	Sodium Chloride 0.9% 1000mL over 24hours

2	**Aprepitant**	**80mg**	**PO**	
2	**Fluorouracil**	**1000mg/m^2**	**IV**	Sodium Chloride 0.9% 1000mL over 24hours
3	**Aprepitant**	**80mg**	**PO**	
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** 60 minutes before chemotherapy	**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 With 20mmol Potassium Chloride		**IV infusion 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 With 20mmol Potassium Chloride		**IV over 90 minutes**	
1 to 4	**Fluorouracil**	**4000mg/m^2** **(1000mg/m^2/day for 4 days)**	**IV**	Sodium Chloride 0.9% over 4 days (96 hours) via infusion device
2	**Aprepitant**	**80mg**	**PO**	
3	**Aprepitant**	**80mg**	**PO**	

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 (Onset: 7-10 days, Nadir: 9-14 days, Recovery: 21-28 days), neutropenia, thrombocytopenia, leucopenia, agranulocytosis, anaemia and pancytopenia

Gastrointestinal: Anorexia, nausea, vomiting and diarrhoea, loss of taste or a metallic taste, stomatitis

Alopecia, loss of fertility.

Cisplatin	
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; It is unclear whether ototoxicity is reversible
Additional side effects	Anaphylactic-like reactions to cisplatin have been reported
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	**Cardiac disorders** <u>Common</u> - Angina, Ischemic ECG abnormalities <u>Uncommon</u> - Arrhythmia, myocardial infarction, myocardial ishchemia myocarditis, dilative cardiomyopathy, cardiac shock.

Investigations and Treatment Plan:

	Pre	C1	C2	C3	C4	Ongoing
Medical Assessment	X		X		X	Alternate cycles
Nursing Assessment		X	X	X	X	Every cycle
FBC	X		X	X	X	Every cycle
U&E & LFT	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				X	After cycle 3
Informed Consent	X					
ECG	X					If clinically indicated
Blood pressure measurement	X					If clinically indicated
PS recorded	X	X	X	X	X	
Toxicities documented	X	X	X	X	X	
Weight recorded	X	X	X	X	X	Every cycle

Dose Modifications and Toxicity Management:

Recommended dose reduction for toxicity management	Cisplatin	Fluorouracil
First dose reduction	60mg/m^2	750mg/m^2
Second dose reduction	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

Hepatic impairment:

Cisplatin: No dose reduction necessary.

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

Renal impairment:

GFR (mL/min)	**Cisplatin**	**Fluorouracil**
Above 60	80mg/m^2 (100% dose)	100% dose
45 to 59	60mg/m^2 (75% dose)	100% dose
Below 45	Consider carboplatin	Consider reduction if CrCl below 30mL/min

References:

Cisplatin 1 mg/ml Sterile Concentrate, Summary of Product Characteristics Hospira UK Ltd Warwickshire.06/09/1996. Available from https://www.medicines.org.uk/emc 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 - updated January 2009)

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

Penile cancer: current therapy and future directions
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Cisplatin and 5-fluorouracil in inoperable, stage IV squamous cell carcinoma of the penis
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