Systemic Anti-Cancer Treatment Protocol

CISPLATIN AND GEMCITABINE
Head and Neck Cancer

PROCEDURE REF: MPHACISGEM
(Version No: 1.2)

Approved for use in:

Induction chemotherapy before concurrent chemo-radiation for loco-regionally advanced nasopharyngeal carcinoma

Recurrent or metastatic nasopharyngeal carcinoma – first line 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
Gemcitabine	**1000mg/m^2**	IV infusion	Days 1 and 8 of 21 day cycle

Neo-adjuvant (Induction chemotherapy) - Repeat at 21 day intervals for 3 cycles

Recurrent or metastatic nasopharyngeal carcinoma - Repeat at 21 day interval for up to 6 cycles

Supportive Treatments:

Fosaprepitant 150mg IV pre chemotherapy

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: IRRITANT- 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

Gemcitabine: NEUTRAL

Refer to the CCC policy for the 'Prevention and Management of Extravasation Injuries'.

Administration:

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

Day	Drug	Dose	Route	Diluent and rate
1	**Fosaprepitant** Immediately prior to hydration	**150mg**	**IV**	100mL Sodium Chloride 0.9% over 30 minutes
	Ondansetron tablets 30mins before chemotherapy	**16mg**	**PO**	
	Dexamethasone tablets 30mins before chemotherapy	**12mg**	**PO**	
	Furosemide tablets	**20mg**	**PO**	
	Sodium Chloride 0.9% 500mL		**IV**	Over 30 minutes
	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**	
	Gemcitabine	**1000mg/m^2**	**IV**	Sodium Chloride 0.9% 250mL over 30 minutes
8	**Gemcitabine**	**1000mg/m^2**	**IV**	Sodium Chloride 0.9% 250mL over 30 minutes

As with all platinum based chemotherapy, patients may experience allergic reaction during administration. Please refer to the CCC Hypersensitivity; Management Prevention Policy.

For severe reactions, discuss with Consultant before continuing with treatment.

It should be strongly noted that patients who have severe reactions should not be re-challenged.

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
Gemcitabine	
Constipation, alopecia, peripheral oedema, rash, influenza-like symptoms, dizziness during infusion, peripheral neuropathy, stomatitis. Elevated liver function tests, haematuria and proteinuria.	

Investigations and treatment plan:

	Pre	Cycle 1	Cycle 2	Cycle 3	Ongoing
Clinical Assessment	X			X	At end of treatment
SACT Assessment (to include PS and toxicities)		X	X	X	Every cycle
FBC	X		X	X	Every cycle
U&E,Mg & LFT	X		X	X	Every cycle
Calculate CrCl (Cockcroft and Gault formula)	X	X	X	X	Every cycle
CT scan	X				As clinically indicated
Informed Consent	X				
Weight recorded	X	X	X	X	Every cycle
Height	X				

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

Gemcitabine	Recommended dose reduction for toxicity management
First dose reduction	800mg/m^2/day
Second dose reduction	Omit day 8

Haematological Toxicity:

Proceed on day 1 and day 8 if-

ANC ≥ 1.0 x 10^9/L	Plt ≥ 100 x 10^9/L

Day 1: delay 1 week and consider dose reduction if-

ANC ≤ 0.9 x 10^9/L	Plt ≤ 99 x 10^9/L

Day 8: omit day 8 if:

ANC ≤ 0.9 x 10^9/L	Plt ≤ 99 x 10^9/L

Hepatic impairment:

Cisplatin
No dose reduction necessary.

Gemcitabine
Bil ≥ 27µmol/L- start at 80% of the original dose and increase the dose if tolerated or start with full dose with active monitoring

Renal impairment:

Cisplatin: CrCl (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.	

Gemcitabine
GFR ≥ 30ml/min: no dose adjustment is needed GFR < 30 ml/min: no need for dose adjustment is expected Haemodialysis (HD): no need for dose adjustment is expected. Start HD 6-12 h after administration.

References:

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

Li Zhang et al. Gemcitabine plus cisplatin versus fluorouracil plus cisplatin in recurrent or metastatic nasopharyngeal carcinoma: a multicentre, randomized, open-label, phase 3 trial. Lancet on line 23rd August 2016.

Li Zhang et al. Gemcitabine and cisplatin induction chemotherapy in nasopharyngeal carcinoma. NEJM 2019; 381:1124-35. DOI: 10.1056/NEJMoa1905287

Supplement to: Krens S D, Lassche, Jansman G F G A, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. Lancet Oncol 2019; 20: e201–08.