Systemic Anti Cancer Treatment Handbook

Cyclophosphamide, Cisplatin and Doxorubicin (CAP)

GUIDELINE REF: MPHACAPHN
(Version No: 1.0)

Approved for use in:

Salivary gland carcinoma

Creatinine clearance at baseline >50ml/min

PS 0-2

Dosage:

Drug	Dosage	Route	Frequency
Cyclophosphamide	500mg/m^2	IV	Repeat at 21 day intervals max 6 cycles
Cisplatin	80mg/m^2	IV	Repeat at 21 day intervals max 6 cycles
Doxorubicin	50mg/m^2	IV	Repeat at 21 day intervals max 6 cycles

Supportive treatments:

Fosaprepitant 150mg pre chemotherapy

Dexamethasone 4mg oral tablets twice daily for 3 days

Cyclizine 50mg three times a day for 7 days

Extravasation risk:

Doxorubicin: vesicant. Erythematous streaking along the vein proximal to the site of injection has been reported, and must be differentiated from an extravasation event. This reaction usually subsides within 30 minutes.

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. Treatment – consider hyaluronidase, topical hydrocortisone cream, warm compression

Cyclophosphamide – Neutral

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)**

Day	Drug	Dose	Route	Diluent and rate
1	Fosaprepitant	150mg 30 minutes prior to commencing chemotherapy	IV	IV Followed by saline flush
1	Ondansetron	As prescribed 30 minutes prior to commencing chemotherapy	IV	Bolus
1	Dexamethasone	As prescribed 30 minutes prior to commencing chemotherapy	IV	bolus
1	**Doxorubicin**	**50mg/m^2**	IV infusion	Fast running saline 0.9% flush
1	**Cyclophosphamide**	**500mg/m^2**	IV infusion	
1	Sodium Chloride 0.9%	**500mL**	IV	30 minutes
1	Sodium Chloride	**1000mL** (+ 20mmol		IV over 2

Pre-hydration	0.9%	Potassium + 10mmol magnesium		hours
1	**Cisplatin** in **1000mL** Sodium Chloride 0.9%	80mg/m^2 if urine output > 200mls/hr	IV infusion	IV over **90 minutes**
1 Post-hydration	Sodium Chloride 0.9%	**1000mL** (+ 20mmol Potassium + 10mmol magnesium		IV over 2 hours

As with all platinum based chemotherapy, patients may experience allergic reaction during administration.

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

Main Toxicities:

Haematological	Neutropenia, thrombocytopenia and anaemia.
Gastrointestinal	Nausea, vomiting, constipation, diarrhoea, stomatitis
Cardiotoxicity	Doxorubicin - sinus tachycardia and/or electrocardiogram (ECG) abnormalities such as non-specific ST-T wave changes. Other cardiac events have been reported, included delayed toxicity.
Dermatological	Alopecia, skin changes including reactivation of radiation sites and sun sensitivity, nail changes,
Urological	Red Urine, bladder irritation Encourage an oral fluids intake of 2 litres per day to promote urinary output & prevent chemical cystitis with cyclophosphamide. Urine output of 100ml/hour or greater will help minimize cisplatin nephrotoxicity
Ocular	Watery eyes, gritty and irritated
Ototoxicity	Observed in up to 31% of ppatients, can be unilateral or bilateral and tends to become more frequent and severe with repeated doses; It is unclear whether ototoxicity is reversible.

Other	Nasal stuffiness can occur immediately with administration of cyclophosphamide, if uncomfortable for the patient the drug can be slowed down. Aching veins / cording following administration Neuropathy with cisplatin

Investigations:

	Pre	Cycle 1	Cycle 2	Cycle 3	Ongoing
Medical Assessment	X		X		Every 2nd cycle
Nursing Assessment		X	X	X	Every cycle
FBC	X		X	X	Every cycle, day 1 only
U&E & LFT (including Mg)	X	X	X	X	Every cycle, day 1 only
Calculate CrCl	X	X	X	X	Every cycle
CT scan	X				As clinically indicated
Informed Consent	X				
PS recorded	X	X	X	X	Every visit
Toxicities documented	X	X	X	X	Every visit
Weight recorded	X	X	X	X	Every visit

Dose Modifications and Toxicity Management:

Haematological toxicity

Proceed on day 1 if:-

Platelets ≥ 100	ANC ≥ 1.0

Delay 1 week on day 1 if:-

Platelets ≤ 99	ANC ≤ 0.9

- If Platelets or ANC still below required levels for treatment at week 2, delay treatment again and patient will need assessed and chemotherapy dose reduction by Oncologist

- If patient suffers an episode of Grade 3 febrile neutropenia, discuss with Oncologist

Non-Haematological

Hepatic function:

	Doxorubicin	Cyclophosphamide
Bilirubin µmol/L	**Dose**	**Dose**
20 to 50	50%	100%
51 to 85	25%	75%
Above 85	Omit	Omit

If AST 2-3 x ULN, give doxorubicin 75% dose

If AST >3 x ULN, give doxorubicin 50% dose

Doxorubicin is contraindicated in patients with severe liver function disorder

Cisplatin – No dosage adjustments required for hepatic impairment

Renal Impairment:

Before every cycle, calculate CrCl using Cockcroft and Gault formula. If borderline, an EDTA should be requested.

Cockcroft and Gault formula

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

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

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

Inadequate urine output (< 200mls/hr):

- Administering 500ml Sodium Chloride +/- furosemide 20 - 40mg - furosemide 20 – 40mg orally may also be given if there is a positive fluid balance of 1.5 litres, a weight gain of 1.5kg or symptoms of fluid overload.
- The patient should be asked to drink 2 litres of fluid in the 24hrs following treatment, and to contact the hospital if this is impossible because of problems e.g. nausea and vomiting.

Neurotoxicity:

If patient develops Grade 2 neuropathy or ototoxicity, discuss with Consultant.
Patients with functional hearing loss should have cisplatin omitted; carboplatin AUC 3-5 can be substituted.

Myocardial toxicity may occur at lower cumulative doses in patients with prior mediastinal irradiation or on concurrent cyclophosphamide therapy or with pre-existing heart disease.

Cumulative:-Dose related peripheral sensory neuropathy: Usually occurs after a cumulative dose. It can occur after treatment with cisplatin is completed, and is usually reversible, taking approx 3 – 5 months to recovery.

Hypersensitivity:

Patients who have previously experienced Grade I or II Platinum HSR should be pre-medicated with 45 minutes prior to cisplatin:

- Dexamethasone 20 mg IV in 50 mL NS over 15 minutes (or Hydrocortisone 100mg) 30 minutes prior to cisplatin:
- Chlorphenamine 10 mg IV over 20 minutes

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

References:

https://www.medicines.org.uk/emc/medicine/623/SPC/Cisplatin+1+mg+ml+Sterile+Concentrate/

https://www.medicines.org.uk/emc/medicine/20555/SPC/Doxorubicin+Solution+for+Injection/