Systemic Anti Cancer Treatment Protocol

Cisplatin and Gemcitabine in Bladder Cancer: Full dose

PROCTOCOL REF: MPHAUROCIG
(Version No: 1.1)

Approved for use in:

- Neo-adjuvant treatment of bladder cancer
- Alternative to split dose regimen for locally advanced or metastatic bladder cancer
- Performance status 0 – 1
- Renal function greater than 60mL/min
- If baseline renal function is below 60mL/min use the split dose regimen.
- Consider carboplatin if other co-morbidities such as neuropathy or tinnitus

Dosage:

Full dose:

Drug	Dose	Route	Frequency
Cisplatin	**70mg/m^2**	IV infusion	Day 1 only
Gemcitabine	**1000mg/m^2**	IV infusion	Days 1 and 8

- Every 21 days
- Up to 6 cycles

Supportive treatments:

Aprepitant 125mg one hour before chemotherapy then 80mg once daily on days two and three (for full dose regimen only)

- Dexamethasone 4mg oral tablets twice daily for 3 days from day two following cisplatin
- Ondansetron 8mg oral tablets twice daily for 3 days from day two following cisplatin
- Domperidone 10mg three times a day or as 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.

Gemcitabine: 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 Cockroft and Gault equation**

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

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

Day	Drug	Dose	Route	Diluent and rate
1	**Aprepitant**	**125mg**	**PO**	60 mins before chemotherapy
	Dexamethasone	**12mg**	**PO**	30 mins before chemotherapy
	Ondansetron	**24mg**	**PO**	30 mins before chemotherapy
	Furosemide oral 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 urology team**			
	Cisplatin	**70mg/m^2**	**IV**	Sodium Chloride 0.9% 1000mL over 90 minutes
	Sodium Chloride 0.9% 1000mL With 20mmol Potassium Chloride		**IV over 90 minutes**	
	Gemcitabine	**1000mg/m^2**	**IV**	Sodium Chloride 0.9% 250mL over 30 minutes
8	**Dexamethasone** 30mins before chemotherapy	**8mg**	**PO**	
	Gemcitabine	**1000mg/m^2**	**IV**	Sodium Chloride 0.9% 250mL over 30 minutes

Main toxicities

Thrombocytopenia, neutropenia, anaemia, nausea, vomiting, diarrhoea

Cisplatin	
Cardiac disorders	Arrhythmia, bradycardia, tachycardia
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	
Hepatobiliary	Elevation of liver transaminases (AST and ALT) and alkaline phosphatase, Increased bilirubin, uncommon reports (≥ l/1000 to <1/100), hepatotoxicity, including liver failure.
Urinary symptoms	Haematuria, Mild proteinuria
Gastrointestinal	stomatitis and ulceration of the mouth, constipation
Additional side effects	alopecia, peripheral oedema, rash, influenza-like symptoms, dizziness during infusion, peripheral neuropathy,

Please refer to the electronic medicines compendium for each drug for more information on side effects.

Investigations:

	Pre	Cycle 1	Cycle 1 D8	Cycle 2	Cycle 2 D8	Prior to cycle 3	Cycle 3	Cycle 3 D8	Ongoing
Informed Consent	X								
Clinical Assessment	X						X		As clinically indicated or at the end of treatment
SACT Assessment (to include PS and toxicities)	X	X	X	X	X		X	X	Every cycle
FBC	X	X	X	X	X		X	X	Every cycle
U&E & LFTs & Magnesium	X	X	X	X	X	X	X	X	Every Cycle
CrCl (Cockcroft and Gault)	X	X	X	X	X	X	X	X	Every cycle
CT scan	X								At the end of treatment and if clinically indicated
Blood pressure measurement	X								Repeat if clinically indicated
Weight recorded	X	X		X			X		Every cycle
Height recorded	X								
Blood glucose	X								Repeat if clinically indicated

Dose Modifications and Toxicity Management:

If patient develops Grade 2 neuropathy or ototoxicity, consider changing cisplatin to carboplatin. Discuss with Consultant. Consider dose modifications for intolerable grade 2 or any grade 3 toxicities.

Recommended dose reduction for toxicity management, full dose regimen only	Cisplatin	Gemcitabine
First dose reduction	60mg/m^2	800mg/m^2
Second dose reduction	40mg/m^2	600mg/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 on day 1 if-

ANC ≤ 0.9 x 10^9/L	Plt ≤ 99 x 10^9/L

Proceed on day 8 if-

ANC ≥ 1.0 x 10^9/L	Plt ≥ 75 x 10^9/L

Omit on day 8 if-

ANC ≤ 0.9 x 10^9/L	Plt ≤ 74 x 10^9/L

Omit day 8 treatment if blood results do not meet the above criteria.

These haematological 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:

Gemcitabine
AST elevations do not seem to cause dose limiting toxicities. If bilirubin > 27 µmol/L, initiate treatment with dose of 800mg/m^2.

No dose adjustment is needed for cisplatin in hepatic impairment.

Renal Impairment:

Gemcitabine: CrCl (mL/min)	Dose
>31	1000mg/m^2 (100% dose)
<30	Consider dose reduction – clinical decision.

Cisplatin : CrCl (mL/min)	Dose
>60	100% dose
40 to 60mL/min	switch to split dose regimen
30 to 40mL/min	Refer patient to treating consultant oncologist for treatment review and switch to carboplatin

References:

Cisplatin 1 mg/ml Sterile Concentrate, Summary of Product Characteristics. Available from https://www.medicines.org.uk/emc/product/6111/smpc Last updated 20/01/2020.

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

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Advanced Bladder Cancer (ABC). Meta-analysis collaboration neoadjuvant chemotherapy in invasive bladder cancer - a systematic review and meta-analysis. Lancet 2003; 361: 1927-1934.

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