Systemic Anti Cancer Therapy Protocol

Cisplatin and Gemcitabine Bladder Cancer: Split dose

PROTOCOL REF: MPHACGBLUR
(Version No: 1.0)

Approved for use in:

- First-line locally advanced or metastatic bladder cancer.
- Neoadjuvant treatment of bladder cancer if creatinine clearance is 40 to 60mL/min. prior to treatment or reduces to below 60mL/min on the standard 3 weekly regimen.
- Performance status 0 – 1
- Carboplatin regimen available as alternative for other co-morbidities, such as neuropathy or tinnitus.

Dosage:

Drug	Dose	Route	Frequency
Cisplatin	**35mg/m^2**	IV infusion	Days 1 and 8
Gemcitabine	**1000mg/m^2**	IV infusion	Days 1 and 8

- Up to 4 cycles
- Cycle length:21 days

Supportive treatments:

- 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.

Administration (+/- Counselling Points):

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

Emetogenic risk (if applicable):

Mild/moderate or severely emetogenic.

Extravasation risk (if applicable):

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

Dosing in renal and hepatic impairment:

Renal impairment:

Gemcitabine: CrCl (mL/min)	**Dose**
>31	1000mg/m^2 (100% dose)
<30	Omit

Cisplatin CrCL (mL/min)	**Dose**
40 to 60 mL/min	100%
Below 40	Switch to carboplatin

Hepatic impairment:

Gemcitabine
AST elevations do not seem to cause dose limiting toxicities. If bilirubin > 27 µmol/L, initiate treatment with dose of 800mg/m2.

No dose adjustment is needed for cisplatin in hepatic impairment.

Interactions:

State the main interactions but add a comment for more detailed interactions please refer to the SPC and add a link to the appropriate SPC

Treatment schedule:

Day	Drug	Dose	Route	Diluent and rate
1	**Dexamethasone**	**8mg**	**PO**	30mins before chemotherapy
	Ondansetron	**16mg**	**PO**	30mins before chemotherapy
	Cisplatin	**35mg/m^2**	**IV**	Sodium Chloride 0.9% 1000mL over 90 minutes
	Gemcitabine	**1000mg/m^2**	**IV**	Sodium Chloride 0.9% 250mL over 30 minutes
8	**Dexamethasone**	**8mg**	**PO**	30mins before chemotherapy
	Ondansetron	**16mg**	**PO**	30mins before chemotherapy
	Cisplatin	**35mg/m^2**	**IV**	Sodium Chloride 0.9% 1000mL over 90 minutes
	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 and treatment plan:

	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	30mg/m^2	800mg/m^2
Second dose reduction	25mg/m^2	600mg/m^2

Haematological toxicity (if required):

ANC (x10^9/L)		Platelets (x10^9/L)	Dose
≥1.0	and	≥100	100%
0.5 to1.0	or	51 to100	75%
≤0.5	or	≤50	delay/omit

On day 8 of the cycle if blood results do not meet the above levels the patient will miss that dose and proceed to the next cycle.

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.

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.

Accord Healthcare Limited Middlesex. Gemcitabine 100 mg/ml Concentrate for Solution for Infusion, Summary of Product Characteristics. . Available fromhttps://www.medicines.org.uk/emc/product/2839/smpc. Last updated 18/03/2019.

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)

Managing locally advanced or metastatic bladder cancer. NICE guideline NG2. Feb 2015. Available from pathways.nice.org.uk/pathways/bladder-cancer

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

Von der Maase H, Hansen SW, Roberts JT et al. Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin and cisplatin in advanced or metastatic bladder cancer: results of a large, randomised, multinational, multicentre, phase III study. J Clin Oncol 2000; 18(17): 3068-3077.