Gemcitabine (1000mg/m^2) and CISplatin (70mg/m^2) Therapy- 21 day

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Adjuvant treatment of upper tract urothelial carcinoma	C67	00628a	Hospital

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

CISplatin is administered on day 1 and gemcitabine on days 1 and 8 of a 21 day cycle for 4 cycles unless disease progression or unacceptable toxicity develops.

Facilities to treat anaphylaxis MUST be present when the chemotherapy is administered.

Admin. Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1 and 8	Gemcitabine	1000mg/m^2	IV infusion	250ml NaCl 0.9% over 30mins	Every 21 days
2	1	*CISplatin	70mg/m^2	IV infusion	1000ml NaCl 0.9% over 120mins	Every 21 days

***Pre and post hydration therapy required for CISplatin**
See local hospital policy recommendations.
Suggested prehydration for CISplatin therapy:

1. Administer 10mmol magnesium sulphate ($MgSO_4$) ((+/-KCl 20mmol/L if indicated) in 1000 mL sodium chloride 0.9% over 60 minutes.

Administer CISplatin as described above
Post hydration: Administer 1000 ml 0.9% NaCl over 60mins
Mannitol 10% may be used to as per local policy to induce diuresis, although there is no conclusive evidence that this is required. The routine use of furosemide to increase urine flow is not recommended unless there is evidence of fluid overload.

ELIGIBILITY:

- Indications as above
- Fit to receive adjuvant chemotherapy within 90 days after surgery.
- Adjuvant treatment of muscle invasive or lymph node –positive metastasis- free disease with predominantly transitional cell carcinoma histology
- ECOG 0-1
- Adequate marrow reserve (ANC > 1.5 x 10^9/L, platelets > 100x10^9/L)

EXCLUSIONS:

- Hypersensitivity to gemcitabine, CISplatin or any of the excipients
- CISplatin
  - Pre-existing neuropathies ≥ grade 2
  - Creatinine clearance < 60 mL/min
  - Significant hearing impairment/tinnitus
- Breast Feeding

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist

TESTS:

Baseline tests:

- FBC, renal and liver profile
- Audiometry and creatinine clearance as clinically indicated

Regular tests:

- Day 1: FBC, renal and liver profile
- Day 8: FBC, creatinine

Disease monitoring:

Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant.

Drug	Dose level 0	Dose level -1	Dose level -2
Gemcitabine	1000mg/m^2	750mg/m^2	500mg/m^2
Cisplatin	70mg/m^2	85% of initial dose	75% of initial dose

Haematological:

Prior to commencing a new treatment cycle (i.e. Day 1), ANC must be >1 x 10^9/L and platelets > 100 x 10^9/L

Table 1: Dose modifications for gemcitabine within a cycle (i.e. Day 8)

ANC (x 10^9/L)		Platelet count (x10^9/L)		Other toxicity	Recommended dose of Gemcitabine
≥1	and	≥ 75			100 %
0.5- 1	And/or	50-75			75%
< 0.5	And/or	<50			Omit day 8 dose. Reduce one dose level with all subsequent cycles

Renal and Hepatic Impairment:

Table 2: Dose modification of CISplatin and Gemcitabine in renal and hepatic impairment

Drug	Renal Impairment		Hepatic Impairment
	Cr Cl (ml/min)	Dose	No dose reductions necessary
CISplatin	≥60	100%	
	45-59	75%	
	<45	Consider CARBOplatin- Clinical decision	
Gemcitabine	>30	100%	AST elevations do not seem to cause dose limiting toxicities. If bilirubin > 27 micromol/L, initiate treatment with dose of 800 mg/m^2.
	<30	Consider dose reduction – Clinical decision	

Management of adverse events:

Table 3: Dose Modification of gemcitabine and CISplatin for Adverse Events

Adverse reactions	Recommended dose modification for Cisplatin	Recommended dose modification for Gemcitabine
Grade 3 non-haematological toxicity (except nausea/vomiting)	Reduce by one dose level or withhold	Reduce by one dose level
Grade 4 non-haematological toxicity	Withhold	Withhold or reduce by one dose level
Grade ≥ 3 neurotoxicity	Discontinue, or consider replacing with CARBOplatin	100% dose of gemcitabine
Grade ≥ 2 pneumonitis		Discontinue gemcitabine

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

CISplatin High **(Refer to local policy)**
Gemcitabine Low **(Refer to local policy).**

PREMEDICATIONS:

Pre and post hydration therapy required for CISplatin administration **(Reference local policy or see recommendations above).**

OTHER SUPPORTIVE CARE:

Patient should be encouraged to drink large quantities of liquids for 24 hours after the cisplatin infusion to ensure adequate urine secretion.

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS:

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

- **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated appropriately.
- **Renal Toxicity**: Nephrotoxicity is common with CISplatin. Encourage oral hydration. Avoid nephrotoxic drugs such as aminoglycoside antibiotics. Irreversible renal failure associated with hemolytic uremic syndrome may occur (rare) with gemcitabine. Use caution with pre-existing renal dysfunction.
- **Pulmonary Toxicity**: Acute shortness of breath may occur. Discontinue treatment if drug-induced pneumonitis is suspected.
- **Cardiovascular:** Due to the risk of cardiac and/or vascular disorders with gemcitabine, particular caution must be exercised with patients presenting a history of cardiovascular events.

- **Please refer to NCCP protocol 00283 Gemcitabine Monotherapy-Locally Advanced or metastatic for detailed information on adverse effects/regimen specific complications relating to gemcitabine**

DRUG INTERACTIONS:

- CISplatin may potentiate the nephrotoxic and ototoxic effects of loop diuretics and aminoglycosides so concurrent use should be avoided.
- Current drug interaction databases should be consulted for more information.

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