Gemcitabine (1000mg/m^2) and CISplatin (35mg/m^2) Therapy- 21 day

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Treatment of patients with locally advanced or metastatic transitional cell carcinoma (TCC) of the urothelium in patients with impaired renal function	C67	00622a	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.

Gemcitabine and CISplatin are administered on days 1 and 8 of each 21 day cycle for 4-6 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 and 8	*CISplatin	35mg/m^2	IV infusion	1000ml NaCl 0.9% over 120mins	Every 21 days

***Pre 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

ELIGIBILITY:

- Indications as above
- ECOG 0-2
- 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.

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)	Recommended dose of Gemcitabine
≥1	and	> 75	100 %
≥1	and	50-75	75%
< 1	or	<50	Omit.
Febrile neutropenia requiring antibiotic therapy	**or**	< 25	Reduce dose to 75% of the original cycle initiation dose for 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
Grade ≥ 3 Non-haematological toxicity (except nausea/vomiting)	Therapy with gemcitabine and CISplatin should be withheld (until toxicity has resolved to grade ≤ 1) and may be resumed with dose reduction at discretion of prescribing consultant.
Grade ≥ 2 peripheral neuropathy	Omit CISplatin or consider substituting CISplatin 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-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.

ATC CODE:

Gemcitabine	L01BC05
CISplatin	L01XA01

REFERENCES:

1. Soto Parra H, Cavina R, Latteri F et al. Three-week versus four-week schedule of cisplatin and gemcitabine: results of a randomized phase II study. Ann Oncol 2002; 13:1080.
2. Hussain SA, Palmer DH, Lloyd B et al. A study of split-dose cisplatin-based neo-adjuvant chemotherapy in muscle-invasive baldder cancer. Oncol Lett 2012; 3:855
3. Uptodate Chemotherapy regimens for adjuvant and neoadjuvant treatment of urothelial cancer: Gemcitabine and cisplatin. Accessed Nov 2020. Available at https://www.uptodate.com/contents/image?imageKey=ONC%2F128074&topicKey=ONC%2F85676&search=treatment-protocols-for-bladder-cancer#H2593650258%23H2593650258%23H2593650258&rank=1~150&source=see_link&sp=0Nephrotoxicity Associated with CISplatin EviQ ID: 184 v.3 https://www.eviq.org.au/clinical-resources/side-effect-and-toxicity-management/prophylaxis-and-prevention/184-nephrotoxicity-associated-with-CISplatin
4. Portilla D et al. CISplatin nephrotoxicity. UptoDate. Last updated 03/04/2019. Accessed Oct 2019 https://www.uptodate.com/contents/cisplatin-nephrotoxicity
5. Dosage Adjustment for Cytotoxics in Renal Impairment January 2009; North London Cancer Network. Available at http://londoncancer.org/media/65600/renal-impairment-dosage-adjustment-for-cytotoxics.pdf

6. Dosage Adjustment for Cytotoxics in Hepatic Impairment January 2009;North London Cancer Network. Available at http://londoncancer.org/media/65594/hepatic-impairment-dosage-adjustment-for-cytotoxics.pdf
7. Cisplatin 1mg/ml Concentrate for Solution for Infusion. Summary of Product Characteristics Last updated: 11/03/2019. Accessed Nov 2020. Available at https://www.hpra.ie/img/uploaded/swedocuments/Final%20approved%20SPC%20PA0822.199.001.pdf
8. Gemcitabine 40mg/ml Concentrate for Solution for Infusion Summary of Product Characteristics Last updated: 30/09/2019. Accessed Nov 2020. Available at https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2059-039-004_30092019160211.pdf
9. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V2 2019. Available at: https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/nccp-classification-document-for-systemic-anti-cancer-therapy-sact-induced-nausea-and-vomiting.pdf

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1	18/12/2020		Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.