Gemcitabine (1000mg/m^2) and CISplatin (70mg/m^2) Therapy- 28 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	C67	00282a	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 is administered on day 1, 8 and 15 and CISplatin is administered on day 1 following gemcitabine or day 2 of each 28 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, 8 and 15	Gemcitabine	1000mg/m^2	IV infusion	250ml NaCl 0.9% over 30mins	Every 28 days
2	1	*CISplatin	70mg/m^2	IV infusion	1000ml NaCl 0.9% over 120mins	Every 28 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 10-20mmol/L if indicated) in 1000 mL sodium chloride 0.9% over 60 minutes (4).

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 (5,6).

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
- Breastfeeding

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

Dose modifications for **gemcitabine within a cycle** (i.e. day 8):

Table 1: Dose modifications for gemcitabine within a cycle (i.e. Days 8 and 15)

ANC (x 10^9/L)		Platelet count (x10^9/L)		Other toxicity	Recommended dose of Gemcitabine
>1	and	> 100			100 %
0.5- 1	or	50-100			75%
< 0.5	or	<50			Omit. Do not restart treatment until ANC > 0.5 and platelets > 50
ANC < 0.5 for > 5 days **or** ANC < 0.1 for > 3 days **or** Any incidence of febrile neutropenia	**or**	< 25	**Or**	cycle delay of >1 week due to any toxicity	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
CISplatin	**Cr Cl (ml/min)**	**Dose**	No dose reductions necessary
	≥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, use dose of 800 mg/m^2 and increase dose to full dose if tolerated.
	<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	Substitute CARBOplatin AUC 5 or 50% reduction of CISplatin dose after recovery to grade ≤ 1. 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 **(Refer to 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.

Gemcitabine:

- **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.
- **Infusion time:** Infusion time prolonged beyond 60 minutes has been shown to increase volume of distribution and has been associated with an increase in toxicity. However, given in the context of a fixed dose rate (FDR) regimen, prolonged infusions have also been reported to produce a higher response rate than standard regimens in association with a higher intracellular accumulation of its active metabolite (dFdCTP) (9-12).

CISplatin:

- Ototoxicity and sensory neural damage should be assessed by history prior to each cycle**.**

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.

REFERENCES:

1. 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, randomized, multinational, multicenter, phase III study. J Clin Oncol 2000; 18(17):3068-77.
2. Vale C. Neoadjuvant chemotherapy in invasive bladder cancer: a systematic review and meta-analysis. Lancet 2003; 361:1927-34.
3. Advanced Bladder Cancer (ABC) Meta-analysis Collaboration. Neoadjuvant chemotherapy in invasive bladder cancer: update of a systematic review and meta-analysis of individual patient data advanced bladder cancer (ABC) meta-analysis collaboration. Eur Urol 2005; 48(2):202-5; discussion 205-6.
4. Irish Medication Safety Network: Best Practice Guidelines For the Safe Use of Intravenous Potassium in Irish Hospitals Available **here.**
5. Nephrotoxicity 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
6. Portilla D et al. CISplatin nephrotoxicity. UptoDate. Last updated 03/04/2019. Accessed Oct 2019 https://www.uptodate.com/contents/cisplatin-nephrotoxicity
7. Dosage Adjustment for Cytotoxics in Renal Impairment January 2009; North London Cancer Network.
8. Dosage Adjustment for Cytotoxics in Hepatic Impairment January 2009; North London Cancer Network.
9. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V3 2021. 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
10. Veltkamp SA, Beijnen JH, Schellens JHM. Prolonged versus standard gemcitabine infusion: translation of molecular pharmacology to new treatment strategy
11. Pollera CF, Ceribelli A, Crecco M, et al. Prolonged infusion gemcitabine: a clinical phase I study at low- (300 mg/m2) and high-dose (875mg/m2) levels. Invest New Drugs 1997; 15 (2):115-121.
12. Kwan P, Mukhopadhyay P, Rastogi A, et al. A novel administration of gemcitabine (via constant dose rate) in combination with docetaxel in advanced non-small cell lung cancer. Proceedings of the American Society of Clinical Oncology 2000; 19:507a (abstract 1985).
13. Dragovich T, Ramanathan RK, Remick S, et al. Phase II trial of a weekly 150-minute gemcitabine infusion in patients with biliary tree carcinomas. Proceedings of the American Society of Clinical Oncology 2000;19:296a (abstract 1159
14. CISplatin 1mg/ml Concentrate for Solution for Infusion. Summary of Product Characteristics. Last updated: 13/10/2021. Accessed Oct 2021. Available at: https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA0822-199-001_13102021113634.pdf
15. Gemcitabine 40mg/ml Concentrate for Solution for Infusion Summary of Product Characteristics. Last updated: 02/10/2020. Accessed Oct 2021. Available at: https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA1380-182-001_02102020144836.pdf

Version	Date	Amendment	Approved By
1			Prof Maccon Keane
2	15/11/2017	Updated title and dosing in renal and hepatic impairment. Applied new NCCP regimen template	Prof Maccon Keane
3	06/11/2019	Reviewed. Update of adverse events.	Prof Maccon Keane
4	18/11/2021	Reviewed. Updated CISplatin prehydration. Updated dose modification of gemcitabine in hepatic impairment. Updated Adverse effects.	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.