Gemcitabine (1000mg/m^2) and CISplatin (25mg/m^2) Therapy - 21 day

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Locally advanced or metastatic pancreatic carcinoma	C25	00383a	Hospital
Locally advanced or metastatic biliary tree carcinoma	C22/C23	00383b	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 day 1 and day 8 of a 21 day cycle and treatment is continued until 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	[1]CISplatin	25mg/m^2	IV infusion	1000ml NaCl 0.9% over 120mins	Every 21 days

[1]**Prehydration therapy required for CISplatin**
See local hospital policy recommendations.
Suggested prehydration for CISplatin therapy:

1. Administer 10mmol magnesium sulphate (MgSO4) (+/-KCl 10-20mmol/L if indicated) in 1000 mL sodium chloride 0.9% over 60 – 120 minutes. (Refer to relevant local hospital policy for advice on administration of electrolyte infusions).

Administer CISplatin as described above

ELIGIBILITY:

- Indications as above
- ECOG 0-2
- Adequate marrow reserve (ANC >1.5x10^9/L, platelets >100x10^9/L)
- Total bilirubin ≤ 1.5xULN, liver enzymes ≤ 5xULN

EXCLUSIONS:

- Hypersensitivity to gemcitabine, CISplatin or any of the excipients
- Patients with inadequate renal function (CrCl <45ml/min)
- 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:

Table 1: Dose modification of Gemcitabine in haematological toxicity

ANC ($x10^9$/L)		Platelets ($x10^9$/L)	Dose
≥1.0	and	>100	100% Dose
0.5 to 0.99	or	50-100	75%
<0.5	or	<75	Omit*
*CISplatin also omitted			

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	50%	
	<45	Delay*	
Gemcitabine	>30	100%*	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.	
*Delay both Cisplatin and gemcitabine if day 1; if day 8, omit CISplatin			

Management of adverse events:

Table 3: Dose Modification schedule 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 **(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 with gemcitabine 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) (8-11).

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. Valle JW, Wasan H, et al; Gemcitabine alone or in combination with CISplatin in patients with advanced or metastatic cholangiocarcinomas or other biliary tract tumours: a multicentre randomised phase II study – The UK ABC-01 Study. Br J Cancer 2009; 101: 621 – 627.
2. Valle JW, Wasan H et al; CISplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Engl J Med 2010;362(14):1273-81.
3. 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
4. Portilla D et al. CISplatin nephrotoxicity. UptoDate. Last updated 03/04/2019. Accessed Oct 2021 https://www.uptodate.com/contents/cisplatin-nephrotoxicity
5. Dosage Adjustment for Cytotoxics in Renal Impairment January 2009; North London Cancer Network.
6. Dosage Adjustment for Cytotoxics in Hepatic Impairment January 2009;North London Cancer Network.

7. 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
8. Veltkamp SA, Beijnen JH, Schellens JHM. Prolonged versus standard gemcitabine infusion: translation of molecular pharmacology to new treatment strategy
9. 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.
10. 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).
11. 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)
12. 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
13. Gemcitabine 40mg/ml Concentrate for Solution for Infusion Summary of Product Characteristics. Last updated: 02/09/2021. 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, CISplatin hydration and dosing in renal and hepatic impairment. Applied new NCCP regimen template	Prof Maccon Keane
3	06/11/2019	Reviewed. Update of adverse events, emetogenic potential	Prof Maccon Keane
4	10/12/2020	Update of renal and hepatic dose modification table	
5	18/11/2021	Updated CISplatin prehydration. Updated Dose modification of gemcitabine in haematological toxicity and in renal and hepatic impairment. Updated adverse effects.	Prof Maccon Keane
6	08/02/2024	Amended CISplatin infusion volume Updated suggested hydration therapy for cisplatin	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.