Cisplatin and Gemcitabine (bladder)

Indication

Palliative therapy for locally advanced or metastatic bladder cancer in patients with good renal function.
Palliative therapy for urothelial transitional cell cancer.
Neo-adjuvant chemotherapy in transitional cell cancer of urinary bladder.

ICD-10 codes

Codes pre-fixed with C67

Regimen details

Day	Drug	Dose	Route
1 and 8	Gemcitabine	1000 mg/m²	IV infusion
1	Cisplatin	70mg/m^2	IV infusion

Cycle frequency

21 days

Number of cycles

Maximum of 6 cycles (palliative treatment)
Usually 3-4 cycles (neo-adjuvant treatment)

Administration

Day 1

Gemcitabine is administered in 250-500mL sodium chloride 0.9% over 30 minutes.

Cisplatin is administered in 500mL sodium chloride 0.9% over 60 minutes following the pre and post hydration protocol below.

Infusion Fluid & Additives	Volume	Infusion Time
Sodium Chloride 0.9%	1000mL	60 minutes
Mannitol 20% **OR** Mannitol 10%	200mL 400mL	10 minutes 15 minutes
Ensure urine output > 100mL / hour prior to giving cisplatin. Give a single dose of furosemide 20mg iv if necessary.		
Cisplatin	500mL	60 minutes
Sodium Chloride 0.9% + 2g $MgSO_4$ + 20mmol KCl	1000mL	2 hours
TOTAL	**2700 or 2900mL**	**4 hours 10 minutes or 4 hours 15 minutes**

Note: Patients with magnesium or potassium below the normal range should have 2g $MgSO_4$ and 20mmol KCl added to the pre-hydration bag and the duration of the infusion increased to 2 hours.

Patients should be advised to drink at least 2 litres of fluid over the 24 hours following cisplatin.

Day 8
Gemcitabine administered in 250-500mL sodium chloride 0.9% over 30 minutes.

Pre-medication
Antiemetics as per local guidelines.

Emetogenicity
Day 1 has severe emetic potential.
Day 8 has moderate - low emetic potential.

Additional supportive medication
Loperamide if required.
H_2 antagonist or proton pump inhibitor if required.
Mouthwashes as per local policy.
If magnesium levels < normal reference range refer to local magnesium replacement guidelines.

Extravasation
Cisplatin – exfoliant (Group 4)
Gemcitabine – neutral (Group 1)

Investigations – pre first cycle

Investigation	**Validity period** (or as per local practice)
FBC	96 hours
U+E (including creatinine)	96 hours
LFTs	14 days
Calcium	14 days
Magnesium	14 days

Investigations – pre subsequent cycles

Investigation	**Validity period** (or as per local practice)
FBC	96 hours (within 24 hours for day 8)
U+E (including creatinine)	96 hours
LFTs	7 days
Magnesium	7 days
Calcium	7 days

In addition FBC is required on day 8 prior to gemcitabine

Standard limits for administration to go ahead
If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant

Investigation	**Limit**
Neutrophils	≥1.0 x 10^9/L
Platelets	≥100 x 10^9/L
Creatinine Clearance (CrCl)	> 60 mL/min
Bilirubin	<1.5 x ULN
ALT/AST	<3 x ULN or < 5 x ULN in presence of liver metastases
Alkaline phosphatase	<2 x ULN

Dose modifications

- **Haematological toxicity**

Day 1

If neutrophils < 1.0 x 10^9/L and/or platelets < 100 x 10^9/L delay by 1 week and recheck FBC.

Reduce cisplatin and gemcitabine to 75% doses if:

- treatment is delayed for > 2 weeks due to haematological toxicity
- grade 4 neutropenia with fever
- grade 4 thrombocytopenia > 3 days
- thrombocytopenia with bleeding
- afebrile grade 4 neutropenia (add prophylactic ciprofloxacin 500mg BD for 7 days for subsequent cycles)

Day 8

Neutrophils (x 10^9/L)		**Platelets** (x 10^9/L)	**Gemcitabine dose**
≥ 1.0	And	≥ 100	100%
0.5 – 1.0	Or	50-99	75%
<0.5	Or	< 50	Omit

- **Renal impairment**

CrCl (mL/min)	**Cisplatin dose**	**Gemcitabine dose**
≥ 60	100%	100%
50 - 59	75%	100%
40 – 49	50%	100%
< 40	Omit or switch to carboplatin AUC 5 (carboplatin is contraindicated if CrCl < 20mL/min)	100%*

*If CrCl <30mL/min consider gemcitabine dose reduction.

- **Hepatic impairment**

Use gemcitabine in caution in hepatic impairment.
Raised transaminases do not seem to cause dose limiting toxicity.
If bilirubin > 1.5 x ULN, initiate gemcitabine at dose of 800 mg/m2.

- **Other toxicities**

Toxicity	**Definition**	**Cisplatin dose**	**Gemcitabine dose (days 1 and 8)**
Neurotoxicity	≤Grade 1	100%	100%
	Grade 2	50%	100%
	Grade 3	Omit or switch to carboplatin AUC 5	100%
	Grade 4	Discontinue	Discontinue
Stomatitis/Mucositis	Grade 1	100%	100%
	Grade 2	Omit until ≤ grade 1 then 75% dose	Omit until ≤ grade 1 then 75% dose
	Grade 3	Omit until ≤ grade 1 then 50% dose	Omit until ≤ grade 1 then 50% dose
	Grade 4	Discontinue or omit until ≤ grade 1 then 50% dose	Discontinue or omit until ≤ grade 1 then 50% dose
Other toxicities (except alopecia or nausea and vomiting)	≤Grade 2	100% (with or without treatment delay)	100%(with or without treatment delay)
	≤Grade 3	Delay until recovery then consider dose reduction (consultant decision)	Delay until recovery then consider dose reduction (consultant decision)

Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects**

Myelosuppression
Infertility
Interstitial pneumonitis, ARDS
Cardiotoxicity
Hepatotoxicity
Haemolytic uraemic syndrome*
Ocular toxicity
Ototoxicity
Nephrotoxicity
Peripheral neuropathy

*Gemcitabine should be discontinued at the first sign of microangiopathic haemolytic anaemia (such as rapidly falling haemoglobin with concomitant thrombocytopenia, elevated bilirubin, creatinine, blood urea nitrogen or LDH. Renal failure may not be reversible with discontinuation of therapy, dialysis may be required.

- **Frequently occurring side effects**

Myelosuppression
Nausea and vomiting
Mucositis, stomatitis
Diarrhoea, constipation
Oedema
Haematuria

- **Other side effects**

Raised transaminases
Alopecia
Fatigue

Significant drug interactions – for full details consult product literature/ reference texts

Warfarin/coumarin anticoagulants: increased or fluctuating anticoagulant effects. Avoid if possible, consider switching patient to a low molecular weight heparin during treatment or if the patient continues taking an oral anticoagulant monitor the INR at least once a week and adjust dose accordingly.

Cisplatin only:
Aminoglycoside antibiotics: increased risk of nephrotoxicity and ototoxicity when given within 2 weeks of cisplatin.
Diuretics: increased risk of nephrotoxicity and ototoxicity
Nephrotoxic drugs: increased nephrotoxicity ; not recommended
Ototoxic drugs: increased risk of ototoxicity
Phenytoin: cisplatin reduces absorption and efficacy of phenytoin, monitor levels and adjust dose as necessary.
Anti-gout agents: cisplatin may increase plasma concentration of uric acid therefore dose adjustments may be required to control hyperuricaemia and gout.

Additional comments

References

- Summary of Product Characteristics Cisplatin (Hospira) accessed via www.medicines.org.uk (13 Jan 2016)
- Summary of Product Characteristics Gemcitabine (Lilly) accessed via www.medicines.org.uk (13 Jan 2016)
- 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.

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