Gem-Cisp: Gemcitabine/Cisplatin in Neoadjuvant and Palliative Bladder Cancer

Indication:
1) Neoadjuvant alternative therapy to M-VAC in patients with Transitional Cell Carcinoma of the Bladder
2) Palliative alternative therapy to M-VAC in patients with Transitional Cell Carcinoma of the Bladder

Regimen details:
- Gemcitabine 1000mg/m² IV D1, D8
- Cisplatin 70mg/m² IV D1

Administration:
- Furosemide 40mg orally
- **Gemcitabine** in 250 - 500ml Sodium Chloride 0.9% IV infusion over 30 min (depending on contract for Dose banding product)
- 1 litre Sodium Chloride 0.9% + 20mmol KCl + 1g MgSO₄ IV infusion over 60 minutes
- **Cisplatin**, in 1 litre Sodium Chloride 0.9% IV over 2 hours
- 1 litre Sodium Chloride 0.9% + 40mmol KCl + 1g MgSO₄ IV infusion over 2 hours
- Then *either* 500ml Sodium Chloride 0.9% IV infusion over 60 minutes *or* 500ml drinking water
- Any device containing aluminium that may come in contact with Cisplatin must be avoided
- *Follow local guidance on Hydration schedules & fluid balance monitoring for outpatient Cisplatin regimens*

Frequency:
- Neoadjuvant setting: every 21 days, for a maximum of 4 cycles
- Palliative setting: every 21 days, for a maximum of 6 cycles

Extravasation:
- Gemcitabine and Cisplatin: Non-vesicants

Anti-emetics:
- Day 1: Highly emetogenic
- Day 8: Low emetogenic
- Follow Local Anti-emetic policy

Regular investigations:
- FBC D1,D8
- U&Es D1
- LFTs D1
- Mg²⁺ and Ca²⁺ D1
- EDTA Prior to 1st cycle (only if necessary)
- Disease evaluation Every 2 cycles

Comments:
- **Hydration - Cisplatin**
- Encourage oral hydration during treatment; for instance, drink a glass of water every hour during treatment, and at least a further 2 litres over the 24 hours following treatment
- Weight should be recorded prior to and at the end of Cisplatin treatment, and a strict fluid balance chart should be maintained. An average urine output of at least 100ml/hr must be maintained throughout treatment, and Cisplatin infusion should not be commenced unless this urine output is achieved. For low urine output, consider increasing the pre-hydration and diuretic regimen. Consider adding diuretics in weight-gain of 1.5 kg, or symptoms of fluid overload
Electrolyte disturbances – Cisplatin
Disturbances in electrolytes can be a long term manifestation due to the Cisplatin induced renal tubular dysfunction. Check electrolytes- additional supplementation of magnesium, calcium or potassium may be required

Allergy – Cisplatin
Anaphylactic-like reactions to Cisplatin have been reported. Facial edema, bronchoconstriction, tachycardia and hypotension may occur within minutes of Cisplatin administration. Adrenaline, corticosteroids and antihistamines have been effectively employed to alleviate symptoms

Haemolytic anaemia – Gemcitabine
Gemcitabine should be discontinued at the first signs of any evidence of micro-angiopathic haemolytic anaemia, such as rapidly falling haemoglobin with concomitant thrombocytopenia, elevation of serum bilirubin, serum creatinine, blood urea nitrogen, or LDH, which may indicate development of haemolytic uraemic syndrome. Renal failure may not be reversible, even with discontinuation of therapy, and dialysis may be required

DOSE MODIFICATIONS

Haematological Toxicity

Neoadjuvant and Palliative setting

Day 1

WBC < 3.0 x 10^9/L    Delay for 1 week.
 or
Neutrophils < 1.0 x 10^9/L
 or
Platelets < 100 x 10^9/L

If Platelets < 25 x 10^9/L for more than 3 days or with bleeding, give Gemcitabine and Cisplatin at 75% doses

Day 8

<table>
<thead>
<tr>
<th>Neutrophils</th>
<th>Platelets</th>
<th>Gemcitabine Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 1.0 x 10^9/L and &gt; 100 x 10^9/L</td>
<td>Give 100%</td>
<td></td>
</tr>
<tr>
<td>0.5 – 1.0 x 10^9/L or 50 – 100 x 10^9/L</td>
<td>Give 75%</td>
<td></td>
</tr>
<tr>
<td>&lt; 0.5 x 10^9/L or &lt; 50 x 10^9/L</td>
<td>Omit. Do NOT defer</td>
<td></td>
</tr>
</tbody>
</table>

Renal Impairment:  GFR should be calculated using the Cockcroft & Gault equation in all patients; if the calculated GFR < 60 or > 120ml/min, measure EDTA clearance or creatinine clearance before prescribing. Monitor trends in serum creatinine between treatments: if 25% from baseline value, re-calculate GFR using the Cockcroft & Gault equation
Gemcitabine should be used with caution in patients with impaired renal function:

<table>
<thead>
<tr>
<th>CrCl (ml/min)</th>
<th>Gemcitabine Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 30</td>
<td>Give 100%</td>
</tr>
<tr>
<td>&lt; 30</td>
<td>Consider dose reduction. Discuss with Consultant</td>
</tr>
</tbody>
</table>

Cisplatin induces nephrotoxicity, which is cumulative. It is therefore contraindicated in patients with renal impairment. Consider dose reduction following the table below:

<table>
<thead>
<tr>
<th>CrCl (ml/min)</th>
<th>Cisplatin Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 60</td>
<td>Give 100%</td>
</tr>
<tr>
<td>51– 60</td>
<td>Give 75%</td>
</tr>
<tr>
<td>40 – 50</td>
<td>Give 50%</td>
</tr>
<tr>
<td>&lt; 40</td>
<td>Contraindicated. Consider Carboplatin(AUC 5)</td>
</tr>
<tr>
<td>Dialysis</td>
<td>Give 50%</td>
</tr>
</tbody>
</table>

**Hepatic Impairment**

**Gemcitabine:** Use with caution in the presence of hepatic dysfunction
Administration of Gemcitabine in patients with liver metastases or a pre-existing medical history of hepatitis, alcoholism, or liver cirrhosis may lead to exacerbation of the underlying hepatic insufficiency
If Bilirubin > 27µmol/L, initiate treatment with Gemcitabine 800mg/m²
BUT
If Bilirubin > 30µmol/L or ALT/ALP > 3 x ULN (> 5 x ULN if liver metastases are present), treatment should be deferred unless approved by Consultant. These patients are at high risk of potentially fatal sepsis

**Cisplatin:** No dose reduction necessary

**DOSE MODIFICATIONS FOR OTHER TOXICITIES AS APPROPRIATE**

**NEUROTOXICITY/OTOTOXICITY – CISPLATIN**

If patient develops Grade 3 or 4 Neurotoxicity, stop Cisplatin and substitute with Carboplatin AUC5
If patient develops Grade 2 Ototoxicity, consider changing Cisplatin to Carboplatin. Discuss with Consultant

**NON – HAEMATOLOGICAL TOXICITY**

For Grade 3 or 4 Mucosal toxicity, give Gemcitabine and Cisplatin at 75% doses
For any Grade 3 – 4 toxicity, treatment should be deferred until recovery, and then continued with an appropriate dose reduction. Discuss with Consultant
Toxicities:
Myelosuppression; nausea; vomiting; mucositis; diarrhoea; nephrotoxicity; neurotoxicity; ototoxicity; flu-like syndrome; proteinuria and haematuria; elevation of transaminases; allergic skin rash; electrolyte disturbances; peripheral oedema; alopecia (mild)

Drug interactions:
Cisplatin
- Allopurinol, colchicine, probenecid, sulfinpyrazone: increase in serum uric acid concentration
- Cephalosporins, aminoglycosides, amphotericin B: increase nephrotoxic and ototoxic effects of Cisplatin in these organs
- Ciclosporine: excessive immunosuppression, with risk of lymphoproliferation
- Cyclazine, phenothiazines: may mask ototoxicity symptoms
- Furosemide (high doses), hydralazine, diazoxide and propranolol: intensify nephrotoxicity
- Oral anticoagulants: require an increased frequency of the INR monitoring
- Penicillamine: may diminish the effectiveness of Cisplatin
- Phenytoin: reduced epilepsy control

Gemcitabine
- Gemcitabine is radiosensitizer
- Warfarin: increased anticoagulant effect of warfarin

References:

www.medicines.org.uk
Dash A et al. Cancer (2008); 113: 2471-2477
NLCN- Dosage Adjustment for Cytotoxics in Renal Impairment. November 2003
NLCN- Dosage Adjustment for Cytotoxics in Hepatic Impairment. November 2003
GSTT guidelines for treating nausea and vomiting in adult patients. September 2007
GSTT Hydration schedules & fluid balance monitoring for outpatient Cisplatin regimens. July 2005
Stockley’s Drug Interactions. Interactions search: Cisplatin&Gemcitabine. July 08
CTCAE v3.0. August 2006