Gem-Cisp: Gemcitabine/Cisplatin for Advanced or Metastatic Biliary Tract Tumours

Indication: Palliative therapy in patients with Advanced or Metastatic Cholangiocarcinomas and other Biliary Tract Tumours

Regimen details: Gemcitabine 1000mg/m² IV D1, D8
Cisplatin 25mg/m² IV D1, D8

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

Frequency: Repeat every 21 days, for a maximum of 8 cycles, until no further clinical benefit, excessive toxicity or evidence of progression

Extravasation: Gemcitabine and Cisplatin: Non-vesicants

Anti-emetics: Moderate emetogenic. Follow Local Anti-emetic policy

Regular investigations:
FBC D1, D8
LFTs & U&Es D1, D8
Mg²⁺ and Ca²⁺ D1, D8
EDTA Prior to 1st cycle
CT scan Every other cycle
CA 19-9 D1

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

Day 1 and Day 8

<table>
<thead>
<tr>
<th>Neutrophils</th>
<th>Platelets</th>
<th>Gemcitabine Dose</th>
<th>Cisplatin 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>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>Give 100%</td>
<td></td>
</tr>
<tr>
<td>&lt; 0.5 x 10^9/L or &lt; 50 x 10^9/L</td>
<td>Defer 1 week</td>
<td>Defer 1 week</td>
<td></td>
</tr>
</tbody>
</table>

If a Gemcitabine dose reduction to 75% has been made, the dose should be re-escalated to full dose (100%) on the subsequent cycles, upon recovery of haematological toxicity, in order to maintain the dose-intensity of therapy

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>
</tbody>
</table>
| < 40 | Contraindicated. Consider :
- Gemcitabine monotherapy
- GemCarbo (AUC 2)
Discuss with Consultant |
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

NEUROPATHY/ OTOTOXICITY – CISPLATIN

If patient develops Grade 2 Neuropathy or Ototoxicity, consider changing Cisplatin to Carboplatin. Discuss with Consultant

NON – HAEMATOLOGICAL TOXICITY

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; alopecia (mild); mucositis; nausea; vomiting; diarrhoea; proteinuria and haematuria; flu-like syndrome; elevation of transaminases; neurotoxicity; ototoxicity; nephrototoxicity (cumulative); allergic skin rash; peripheral oedema

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
- Clonidine, 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