**Gem-Cisp: Gemcitabine/Cisplatin in Relapsed Ovarian, Fallopian Tube and Primary Peritoneal Cancer**

**Indication:** Second line in Platinum-sensitive patients with Ovarian, Fallopian Tube and Primary Peritoneal Cancer unable to tolerate Paclitaxel

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

(*) Consider starting Cisplatin at 60mg/m² in patients with poor performance status

**Administration:**
- Furosemide 40mg orally
- **Gemcitabine** in 250 - 500ml Sodium Chloride 0.9% IV infusion over 30 min (depending on contract for Dose banding product)
- 1litre 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
- 1litre 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:** 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
- Ca125 Prior to each cycle
- EDTA Prior to 1st cycle (only if necessary)
- Audiogram Prior to 1st cycle, if clinically indicated
- Disease evaluation Every 3 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

Day 1

WBC < 3.0 x 10^9/L
or
Neutrophils < 1.5 x 10^9/L
or
Platelets < 100 x 10^9/L

Delay for 1 week.
Repeat FBC - If within normal parameters, resume treatment with 100% doses

Day 8

Neutrophils
≥ 1.0 x 10^9/L
0.5 – 0.99 x 10^9/L
< 0.5 x 10^9/L

and
50 – 99 x 10^9/L
< 50 x 10^9/L

Platelets
≥ 100 x 10^9/L
50 – 99 x 10^9/L
< 50 x 10^9/L

Gemcitabine Dose
Give 100%
Give 75%
Omit. Do NOT defer

Subsequent cycles

If Neutrophils < 0.5 x 10^9/L for ≥ 7 days, OR
Febrile Neutropenia is diagnosed OR
Platelets < 50 x 10^9/L,

Gemcitabine should be given at 75% dose and Cisplatin dose should be reduced from 70mg/m^2 to 60mg/m^2 (or from 60mg/m^2 to 50mg/m^2)

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>50 – 60</td>
<td>Give 80%</td>
</tr>
<tr>
<td>&lt; 50</td>
<td>Contraindicated. Discuss alternative therapy with Consultant</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**

**NEUROPATHY/ OTOTOXICITY – CISPLATIN**

Cisplatin induced neuropathy is cumulative:

<table>
<thead>
<tr>
<th>Grade</th>
<th>Neuropathy-sensory</th>
<th>Ototoxicity</th>
<th>Cisplatin Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Paresthesia (including tingling) but not interfering with function</td>
<td>-------</td>
<td>Give 100%</td>
</tr>
<tr>
<td>2</td>
<td>Paresthesia interfering with function, but not interfering with activities of daily living</td>
<td>Tinnitus not interfering with activities of daily living</td>
<td>Give 80%</td>
</tr>
<tr>
<td>3</td>
<td>Paresthesia interfering with activities of daily living</td>
<td>Tinnitus interfering with activities of daily living</td>
<td>Omit Cisplatin</td>
</tr>
<tr>
<td>4</td>
<td>Disabling</td>
<td>Disabling</td>
<td>Omit Cisplatin</td>
</tr>
</tbody>
</table>
NON – HAEMATOLOGICAL TOXICITY

For any other 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
- Cyclizine, 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
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
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