**TIP: Paclitaxel / Ifosfamide / Cisplatin in Relapsed Germ Cell Tumour**

**Indication:** Second line therapy in Relapsed Germ Cell Tumours

**Regimen details:**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (mg/m²)</th>
<th>Route</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel</td>
<td>175</td>
<td>IV</td>
<td>D1</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>20</td>
<td>IV</td>
<td>D1- D5</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>1000</td>
<td>IV</td>
<td>D1- D5</td>
</tr>
<tr>
<td>Mesna (**)</td>
<td>1000</td>
<td>IV</td>
<td>D1- D5</td>
</tr>
<tr>
<td>Pegfilgrastim</td>
<td>6</td>
<td>SC</td>
<td>D6</td>
</tr>
</tbody>
</table>

**Administration:**

**Day 1**

- **Paclitaxel** in 500mls Sodium Chloride 0.9% over 3 hours via non-PVC infusion bag, with a 0.22 micron in-line filter. Paclitaxel must be diluted to a concentration of 0.3-1.2mg/ml to maintain stability in clinical practice.
- Furosemide 40mg orally
- 500ml Sodium Chloride 0.9% IV infusion over 60 minutes
- **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
- **Ifosfamide** 1000mg/m² and **Mesna** 500mg/m² given as IV infusion in 1000ml NaCl 0.18% + Glucose 4% over 1 hour
- **Mesna** 500mg/m² IV in 1000ml NaCl 0.9% over 8 hours

**Day 2 to Day 5**

- Furosemide 40mg orally
- 500ml Sodium Chloride 0.9% IV infusion over 60 minutes
- **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
- **Ifosfamide** 1000mg/m² and **Mesna** 500mg/m² given as IV infusion in 1000ml NaCl 0.18% + Glucose 4% over 1 hour
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**Day 6**

- Pegfilgrastim 6mg given subcutaneously

*Follow guidance protocol for Hydration schedules & fluid balance monitoring for outpatient Cisplatin regimens*

**Mesna** is a synthetic compound that protects the bladder from the urotoxic metabolites of the oxazaphosphorine derivatives (e.g. Ifosfamide, Cyclophosphamide). The scheduling is designed to ensure that there is adequate Mesna in the bladder throughout the period when Ifosfamide metabolites are appearing in the urine.

**Premedication:**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (mg)</th>
<th>Route</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexamethasone</td>
<td>20</td>
<td>IV</td>
<td>30 – 60 minutes prior to Paclitaxel administration</td>
</tr>
<tr>
<td>Chlorphenamine</td>
<td>10</td>
<td>IV</td>
<td>30 – 60 minutes prior to Paclitaxel administration over at least 1 minute</td>
</tr>
<tr>
<td>Ranitidine</td>
<td>50</td>
<td>IV</td>
<td>30 – 60 minutes prior to Paclitaxel administration over at least 2 minutes</td>
</tr>
</tbody>
</table>
Frequency: Every 21 days, for 4 – 6 cycles

Extravasation: Paclitaxel: Vesicant
Cisplatin and Ifosfamide: Non-vesicants

Anti-emetics: Highly emetogenic. Follow Local Anti-emetic Policy

Regular investigation:
- FBC D1
- LFTs D1
- U&Es D1
- Mg²⁺ and Ca²⁺ D1
- EDTA Prior to 1st cycle, if clinically indicated
- Audiogram Prior to 1st cycle, if clinically indicated
- Ca 125 Prior to each cycle for female patients
- AFP, HCG, LDH Weekly until normalization, if tumour markers had been previously elevated; 3-weekly thereafter

Comments:
Hydration / Fluid balance – Cisplatin and Ifosfamide
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 - 2 kg, or symptoms of fluid overload or if there is an excessive positive fluid balance (> 1.5 L/Kg from the start of treatment)

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. No further Cisplatin should be given unless within a “desensitising” protocol

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

Encephalopathy – Ifosfamide
Ifosfamide encephalopathy is a serious neurotoxic condition that can develop on any treatment course. In the early stages, it can present with a variety of symptoms such as somnolence and confusion. Any reports of patients being excessively drowsy or confused should be regarded as indicators of Ifosfamide encephalopathy. As this is a progressive condition, discuss with Consultant, discontinue Ifosfamide and institute treatment with Methylene blue immediately. DOSE: Methylene blue 50mg slow iv bolus over 5 minutes, this may need to be repeated up to 6 times/day. Methylene blue is available as a 1% solution, 5ml of 1% solution is equivalent to 50mg. Seek Consultant advise.
Three factors that have also been demonstrated to predispose individuals to this problem are renal impairment, low albumin and large pelvic tumour mass. If a patient has two of the three risk factors, consider discontinue Ifosfamide and institute appropriate supportive therapy. Future treatment needs to be reviewed by the Consultant.

Nephrotoxicity – Ifosfamide
Renal function should be assessed by EDTA clearance, at the start of the treatment, but estimation from serum creatinine levels using the Cockcroft & Gault equation is acceptable if the patient has a stable creatinine concentration and no confounding factors (e.g. catabolic states)
On subsequent cycles, the renal function needs to be re-assessed if there is a 30% change in serum creatinine.

Haemorrhagic cystitis – Ifosfamide
A morning urine specimen should be examined before each scheduled dose of Ifosfamide because of the possibility of Ifosfamide – induced haemorrhagic cystitis. To decrease the incidence and severity of bladder toxicity, adequate hydration, maintenance of fluid balance and a uroprotective agent, Mesna, should be used. In patients who develop microscopic haematuria, despite concurrent use of Mesna, Ifosfamide therapy should be discontinued until the haematuria resolves.

DOSE MODIFICATIONS

Haematological toxicity

| WBC < 1.5 x 10⁹/L | Delay therapy for 3 days |
| or | Repeat FBC every 3 days until these levels are reached, then resume therapy at 100% doses. |
| Neutrophils < 0.5 x 10⁹/L | Consider dose reduction in all drugs if persistent haematological toxicity despite the use of G-CSF. Discuss with Consultant |
| or | |
| Platelets < 50 x 10⁹/L |

Renal Impairment
Paclitaxel: No dose adjustment required. Assess renal function when clinically indicated.

Cisplatin induces nephrotoxicity, which is cumulative. It is therefore contraindicated in patients with renal impairment.

Ifosfamide is not recommended in patients with a Creatinine > 120µmol/L.

Consider doses reduction following the table below:

<table>
<thead>
<tr>
<th>GFR (ml/min)</th>
<th>Cisplatin and Ifosfamide Doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 40</td>
<td>Give 100%</td>
</tr>
<tr>
<td>&lt; 40</td>
<td>Omit</td>
</tr>
<tr>
<td>If recovered to ≥ 40</td>
<td>Re-start at 75%</td>
</tr>
</tbody>
</table>
Hepatic Impairment

**Paclitaxel** is not recommended in severe impaired hepatic function:

<table>
<thead>
<tr>
<th>Bilirubin (µmol/L)</th>
<th>Paclitaxel Dose (mg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 26</td>
<td>Give 100%</td>
</tr>
<tr>
<td>27 – 51</td>
<td>Give 75%</td>
</tr>
<tr>
<td>&gt; 51</td>
<td>Give 50%</td>
</tr>
</tbody>
</table>

**Cisplatin:** No dose reduction necessary

**Ifosfamide** is not recommended in patients with a bilirubin > 17µmol/L or serum transaminases or ALP more than 2.5 x upper normal limit

**DOSE MODIFICATIONS FOR OTHER TOXICITIES AS APPROPRIATE**

**PERIPHERAL NEUROPATHY**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Neuropathy-sensory</th>
<th>Paclitaxel Dose</th>
<th>Cisplatin Dose</th>
<th>Ifosfamide Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Paresthesia (including tingling) but not interfering with function</td>
<td>175mg/m²</td>
<td>20mg/m²</td>
<td>1000mg/m²</td>
</tr>
<tr>
<td>2</td>
<td>Paresthesia interfering with function, but not interfering with activities of daily living</td>
<td>135mg/m²</td>
<td>Omit D5</td>
<td>1000mg/m²</td>
</tr>
<tr>
<td>3</td>
<td>Paresthesia interfering with activities of daily living</td>
<td>Omit Paclitaxel</td>
<td>Consider Carboplatin</td>
<td>1000mg/m²</td>
</tr>
<tr>
<td>4</td>
<td>Disabling</td>
<td>Omit Paclitaxel</td>
<td>Consider Carboplatin</td>
<td>1000mg/m²</td>
</tr>
</tbody>
</table>

**Toxicities:** Myelosuppression; fatigue; nausea; vomiting; mucositis; constipation; diarrhoea; taste disturbance; urotoxicity: haematuria, haemorrhagic cystitis; neurotoxicity; nephrotoxicity; encephalopathy; electrolyte disturbances; arthralgia; myalgia; alopecia

**Drug interactions :**

**Paclitaxel**
- Concomitant administration of inducers or inhibitors of cytochrome P450 Isoenzymes (CYP2C8 and 3A4) e.g. erythromycin, fluoxetine, gemfibrozil, rifampicin, carbamazepine, phenytoin, phenobarbital etc, may alter the pharmacokinetics of Paclitaxel, presenting a theoretical interaction
- Clozapine : avoid concomitant use, increased risk of agranulocytosis

**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

Ifosfamide
- Phenobarbital: may enhance the risk of encephalopathy
- Warfarin: anticoagulant effect of warfarin may be enhanced

References:
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