VIP: Etoposide / Ifosfamide / Cisplatin in Advanced Germ Cell Tumour  
(ONLY to be given at GSTT)

**Indication:**
1) Alternative salvage therapy to BEP in Relapsed Seminomatous Germ Cell Tumour  
2) Alternative salvage therapy to BEP in Relapsed Non-seminomatous Germ Cell Tumour  
3) Alternative first line therapy to BEP in Non-seminomatous Germ Cell Tumour

**Regimen details:**
- **Dual lumen Central Venous Access preferred**
- **Etoposide** 75mg/m^2 IV D1-D5  
- **Cisplatin** 20mg/m^2 IV D1-D5  
- **Mesna** 240mg/m^2 IVbolus D1  
- **Ifosfamide** 1200mg/m^2 IV D1 - D5  
- **Mesna** 1200mg/m^2 IV D1 - D5  
- **Pegfilgrastim** 6mg SC D6

**Administration:**
- **Etoposide** in Sodium Chloride 0.9% IV over 60 minutes  
  Etoposide infusion should have maximum concentration of 0.2 – 0.4 mg/ml (PVC free)  
  Monitor Etoposide infusion for the first 15 minutes for signs of hypotension  
  Furosemide 40mg orally
- **Cisplatin** IV infusion over 1 hour  
  1litre Sodium Chloride 0.9% + 20mmol KCl + 1g MgSO_4 IV infusion over 1 hour  
  *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
- **Mesna** is a synthetic compound that protects the bladder from the urotoxic metabolites of the oxazaphosphorine derivatives (e.g Ifosfamide, Cyclophosphamide) and should be administered as indicated below:
  - **Mesna** 240mg/m^2 at hour 0, is given as an IV Bolus, prior to first dose Ifosfamide infusion  
  - **Ifosfamide** in Sodium Chloride 0.9% IV over 60 minutes  
  - **Mesna** 1200mg/m^2 continuous infusion on days 1 through 5 (infuse at 125ml/hr x 5 days)  
  - **Pegfilgrastim** 6mg subcutaneously on day 6

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

**Frequency:**
Every 21 days, for 4 cycles

**Extravasation:**
Etoposide, Cisplatin and Ifosfamide: Non- vesicants

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

**Regular investigation:**
- **FBC** D1  
- **LFTs** D1  
- **U&Es** D1  
- **Mg^{2+} and Ca^{2+}** D1  
- **EDTA** Prior to 1st cycle (if necessary)  
- **AFP, HCG, LDH** Weekly, if tumour markers had been previously elevated
Comments:

**Hydration / Fluid balance – Cisplatin and Ifosfamide**

Weight should be recorded prior to and at the end of Cisplatin treatment (daily weight), 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. 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 < 3.0 $\times$ 10^9/L or Neutrophils < 1.0 $\times$ 10^9/L or Platelets < 100 $\times$ 10^9/L

Delay therapy for 3 days. Repeat FBC - If within normal parameters resume therapy at 100% in all drugs

Renal Impairment

Etoposide dose should be adjusted as follows:

<table>
<thead>
<tr>
<th>CrCl (ml/min)</th>
<th>Etoposide Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 60</td>
<td>Give 100% dose</td>
</tr>
<tr>
<td>46 – 60</td>
<td>Give 85% dose</td>
</tr>
<tr>
<td>30 – 45</td>
<td>Give 80% dose</td>
</tr>
<tr>
<td>&lt; 30</td>
<td>Give 75% dose</td>
</tr>
<tr>
<td>&lt; 15</td>
<td>Give 50% dose</td>
</tr>
</tbody>
</table>

Subsequent doses are based on clinical response

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</td>
</tr>
<tr>
<td>Dialysis</td>
<td>Give 50%</td>
</tr>
</tbody>
</table>

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

Ifosfamide dose should be adjusted as follows:

<table>
<thead>
<tr>
<th>GFR (ml/min)</th>
<th>Ifosfamide Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 60</td>
<td>100%</td>
</tr>
<tr>
<td>40 – 59</td>
<td>70%</td>
</tr>
<tr>
<td>&lt; 40</td>
<td>Clinical decision</td>
</tr>
</tbody>
</table>

Hepatic Impairment

Etoposide dose should be adjusted as follows:

<table>
<thead>
<tr>
<th>Bilirubin (µmol / L)</th>
<th>AST (units / L)</th>
<th>Etoposide Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 26 or &lt; 60</td>
<td></td>
<td>Give 100%</td>
</tr>
<tr>
<td>26 – 51 or 60 – 180</td>
<td></td>
<td>Give 50 %</td>
</tr>
<tr>
<td>&gt; 51 or &gt; 180</td>
<td></td>
<td>Omit</td>
</tr>
</tbody>
</table>

Cisplatin: No dose reduction necessary

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Reason for Update: Network Protocol Development
Version: 1
Supersedes: All other versions
Approved by Urology Consultant: Hartmut Kristeleit
Date: 29.10.09
Prepared by: Maria Teresa Pacheca-Palomar  May ’09
Checked by (Network Pharmacist): Jacky Turner
Approved by SELCN DTAC Chair: Nic Ketley
Date: 29/01/2010
Ifosfamide is not recommended in patients with a bilirubin > 21 µmol/L or serum transaminases or ALP more than 2.5 x upper normal limit

**Toxicities:**
Bone marrow suppression (severe): Neutropenia; leucopenia; thrombocytopenia; nausea; vomiting; infection; urotoxicity: haematuria, haemorrhagic cystitis; neurotoxicity; alopecia; nephrotoxicity; electrolyte disturbances

**Drug interactions:**

**Etoposide**
- Aprepitant: elevated Etoposide plasma levels
- Ciclosporin (high doses): increased plasma concentration of Etoposide, increased risk of toxicity
- Coumarins: enhanced anticoagulant effect
- Glucosamine; St John’s Wort: possible reduced Etoposide effectiveness
- Grapefruit juice: reduced Etoposide plasma levels
- Phenytoin: reduced absorption of the antiepileptic

**Cisplatin**
- Allopurinol, colchicines, 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
- Cyazine, 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**
- Warfarin: anticoagulant effect of warfarin may be enhanced

**References:**
- www.medicines.org.uk
- GSTT guidelines for treating nausea and vomiting in adult patients. September 2007
- UCLH- Dosage Adjustment for Cytotoxics in Renal Impairment. November 2003
- UCLH- Dosage Adjustment for Cytotoxics in Hepatic Impairment. November 2003
- Stockley’s Drug Interactions. Interactions search: Paclitaxel, Ifosfamide, Cisplatin. May’09
- CTCAE v3.0. August 2006