## Topotecan and Cisplatin for Recurrent or Stage IVb Cervical Cancer

**Indication:**  
Palliative therapy for Recurrent or Stage IVb Cisplatin-naïve Cervical Cancer patients

**Regimen details:**  
<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topotecan</td>
<td>0.75mg/m²</td>
<td>IV</td>
<td>D1 – D3</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>50mg/m²</td>
<td>IV</td>
<td>D1</td>
</tr>
</tbody>
</table>

**Administration:**  
- **Topotecan**, by IV infusion, in 50 - 100ml Sodium Chloride 0.9% over 30 minutes
- Furosemide 40mg orally
- 1 litre 0.9% Sodium Chloride + 20 mmol 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

*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:**  
Every 21 days for a maximum of 6 cycles

**Extravasation:**  
Topotecan and Cisplatin: Non-vesicants

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

**Regular investigations:**  
- FBC D1
- U&Es D1
- LFTs D1
- Mg²⁺ and Ca²⁺ D1
- EDTA Prior to 1st cycle (only if necessary)
- Audiogram Prior to 1st cycle, if clinically indicated
- CT scan (disease evaluation) After 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.
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 without Consultant approval.

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.

**DOSE MODIFICATIONS**

**Haematological Toxicity**

**D1**

WBC < 3.0 x 10⁹/L or Neutrophils < 1.5 x 10⁹/L or Platelets < 100 x 10⁹/L

Delay therapy for 1 week. Repeat FBC – If within normal parameters, proceed with 100% doses.

Subsequent cycles

If Neutrophils < 0.5 x 10⁹ for ≥ 7 days OR

Febrile neutropenia is diagnosed OR

Platelets < 50 x 10⁹/L,

Topotecan dose should be reduced to 80% from previous dose (Topotecan 0.6mg/m²). If prolonged myelosuppression, despite the use of lower dose, discontinue Topotecan and consider single agent Cisplatin at 60mg/m².

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 >20% from baseline value, re-calculate GFR using the Cockcroft & Gault equation.

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. Consider changing to Carboplatin / Paclitaxel if appropriate</td>
</tr>
</tbody>
</table>

**Reason for Update: Network Protocol Development**

*Approved by Gynaecology Consultant: Anna Winship*

*Supersedes: All other versions Date: 15.01.10*

*Prepared by: M. Teresa Pacheca-Palomar Jan’10 Checked by (Network Pharmacist): Jacky Turner*

*Approved by SELCN DTAC Chair: Nic Ketley Date: 29.01.10*
Topotecan is not recommended to be used in patients with severe impaired renal function

<table>
<thead>
<tr>
<th>GFR (ml/min)</th>
<th>Topotecan 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>Omit</td>
</tr>
</tbody>
</table>

**Hepatic Impairment**

- **Cisplatin**: No dose reduction necessary
- **Topotecan**: There is no experience of Topotecan in patients with severely impaired hepatic function. Discuss with Consultant if regimen appropriate

**DOSE MODIFICATIONS FOR OTHER TOXICITIES AS APPROPRIATE**

**PERIPHERAL 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>

(*) If Grade 2 toxicity persists, despite Cisplatin dose reduction, consider discontinuing regimen or changing to Carboplatin / Paclitaxel at Consultant’s discretion

Patients who experience Grade 3 or Grade 4 Non-haematological toxicity should have Topotecan dosage reduced to 0.6mg/m²/day

**Toxicities:** Myelosuppression; fatigue; nausea; vomiting; constipation; diarrhoea; mucositis; nephrotoxicity; neuropathy/ototoxicity; taste disturbance; electrolyte disturbances; allergic reactions; alopecia
Drug interactions:

Cisplatin
- Allopurinol, colchicine, probenecid, sulfipyrazone: 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, 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

Topotecan
- Clozepine: increased risk of agranulocytosis, avoid concomitant use
- Digoxin tablets: reduced absorption (resolved by giving the digoxin in liquid)
- Phenytoin: may possibly increase Topotecan clearance

References:
www.medicines.org.uk
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