REGIMEN TITLE: Cisplatin Etoposide IV/Oral therapy

Indication: Small cell Lung cancer, Extensive Stage disease (Palliative intent)
First line treatment. Consider Carboplatin for elderly patients with poor PS

Eligible for patients able to tolerate and comply with oral dosage forms.

Regimen details: Cisplatin 80mg/m² IV D1
Etoposide 100mg/m² IV D1, and
200mg/m² PO D2 AND 3

Administration: Furosemide 40mg PO stat
Cisplatin/1 litre 0.9% Sodium Chloride + 20 mmol KCl + 1g MgSO4 IV over 60 minutes
Etoposide IV: Cisplatin in 1 litre 0.9% Sodium Chloride IV over 2 hours
Etoposide in Sodium Chloride 0.9% IV over 60 min (See comments for volume)
Then either 500ml Sodium Chloride 0.9% IV over 60 minutes or 500ml drinking water
*Follow guidance protocol for Hydration schedules & fluid balance monitoring for outpatient cisplatin regimens

Monitor Etoposide infusion for the first 15 minutes for signs of hypotension.

Etoposide Oral: Capsules to be swallowed whole on an empty stomach half an hour before or
2 hours after a meal. Available as 50mg and 100mg capsules. Daily dose of capsules can be divided in two if necessary.

Frequency: 3 weekly cycle - Day 1 to Day 3.
Total of 6 cycles
Assess response after 2 or 3 cycles. Responding patients to continue to 6 cycles.

Anti- emetics: Day 1. High emetogenicity
Days 2 and 3. Low emetogenicity

Regular investigations: FBC D1
LFTs D1
U&Es D1
Mg and Ca D1 (EDTA Prior to 1st cycle)
Audiogram Prior to 1st cycle when clinically indicated
Baseline CT, CXR
Clinical toxicity assessments (including neuropathy & local toxicity)

Comments: 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. 
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.

**Etoposide** infusion should have maximum concentration of 0.2 - 0.35mg/ml. (PVC free)

**Etoposide PO** (days 2 and 3) be supplied to the patient for oral self-administration. 
Ensure that the patient has an information pack and the treatment plan.

**Extravasation**: Non vesicant

**Toxicities:** Nausea and vomiting, Myelosupression- risk of sepsis and thrombocytopenia, Constipation and/or diarrhoea, Hypotension, Moderate alopecia, Peripheral neuropathy, Neurotoxicity (ototoxicity) , Nephrotoxicity, Stomatitis, Fatigue, ovarian failure/ infertility, electrolyte imbalances

*Anaphylactic-like reactions to cisplatin and Etoposide* 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

**Adequate contraceptive methods should be used during therapy.**

**Dose Modifications**

**Haematological Toxicity**

*Defer therapy for 1 week if neutrophils <1.0 x 10⁹/l or platelets <100 x 10⁹/l*

<table>
<thead>
<tr>
<th>Neutrophils x 10⁹/l</th>
<th>Platelets x 10⁹/l</th>
<th>Cisplatin Dose</th>
<th>Etoposide dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1.5</td>
<td></td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>1.0-1.49</td>
<td>≥100</td>
<td>100%</td>
<td>75%</td>
</tr>
<tr>
<td>&lt;1.0</td>
<td>&lt; 100</td>
<td>Delay*</td>
<td>Delay*</td>
</tr>
</tbody>
</table>

**Renal Impairment**

<table>
<thead>
<tr>
<th>CrCl (mL/min)</th>
<th>Etoposide dose</th>
<th>Cisplatin dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>46-60</td>
<td>85% dose</td>
<td>Carboplatin suggested when CrCl &lt;60 ml/min</td>
</tr>
<tr>
<td>30-45</td>
<td>80% dose</td>
<td></td>
</tr>
<tr>
<td>&lt;30</td>
<td>Regimen Contra-indicated</td>
<td></td>
</tr>
</tbody>
</table>

Subsequent doses based on clinical response

<table>
<thead>
<tr>
<th>Reason for Update: Hydration, Etoposide concentration limits</th>
<th>Approved by Consultant: A.Montes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Version: 1.1</td>
<td>Date: 14/08/08</td>
</tr>
<tr>
<td>Supersedes: All other versions</td>
<td>Checked by (Network Pharmacist): J.Turner</td>
</tr>
<tr>
<td>Prepared by: SEestila April08, updated Jan10</td>
<td>Approved by SELCN DTAC Chair: Nick Ketley</td>
</tr>
<tr>
<td>Date: 01/2010</td>
<td>Date: 01/2010</td>
</tr>
</tbody>
</table>
Cisplatin-induced nephrotoxicity is dose-related and cumulative. It manifests early by elevations in blood urea, creatinine, and wasting of potassium and magnesium. Renal function, fluid and electrolyte balance must return to normal prior to subsequent doses. Renal toxicity may be irreversible and is more prolonged and severe with repeated courses. Avoid concomitant use of other nephotoxic drugs (see ‘Drug interactions’).

**Hepatic Impairment**

**Cisplatin:** No dose modifications for hepatic impairment

<table>
<thead>
<tr>
<th>Bilirubin (micromol/L)</th>
<th>AST (units/L)</th>
<th>Etoposide dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>26-51 or 60-180</td>
<td></td>
<td>50% dose</td>
</tr>
<tr>
<td>&gt;51 or &gt;180</td>
<td></td>
<td>Clinical decision.</td>
</tr>
</tbody>
</table>

**Dose modifications for other toxicities as appropriate**

**Neurological toxicity**

Grade 2 neurotoxicity requires a 50% dose reduction of cisplatin. For Grade 3 or 4 neurotoxicity, treatment should be discontinued.

**Other toxicities**

If mucositis or diarrhoea ≥ grade 3 in previous course then give 66% dose of both agents.

Development of severe dysphagia, dehydration, orthostasis or any Grade 4 toxicity is grounds for discontinuation of treatment if therapy delayed more than one week to permit recovery.

**Drug interactions:** Phenytoin, carbamazepine – Cisplatin decreases efficiency

Nephrotoxic drugs (with Cisplatin)

Aminoglycoside antibiotics-increased risk of ototoxicity (with Cisplatin)

Cyclosporin (high doses) increase Etoposide plasma levels/toxicity.

Aprepitant- elevated Etoposide plasma levels

Glucosamine- possible reduced Etoposide effectiveness

St John’s Wort- possible reduced Etoposide effectiveness

Monitor INR levels carefully if on concomitant warfarin

Grapefruit juice- reduced Etoposide plasma levels

References:

[www.medicines.org.uk](http://www.medicines.org.uk), accessed April 08

SELCN Lung Diagnostic & Treatment Guidelines, July 06


SWSHCN Protocols. June 07 version

Micromedex review, accessed April 08