REGIMEN TITLE: Cisplatin Etoposide IV +/- concurrent radiotherapy

Indication: Small cell Lung cancer, Limited Stage disease (Curative intent) Extensive stage disease (palliative intent) for suitable patients First line treatment. Consider Carboplatin for elderly patients with poor PS or tinnitus

Regimen details: Cisplatin 80mg/m² IV D1 Etoposide 120mg/m² IV D1 to D3 *consider lower dose of etoposide if on concurrent radiotherapy Etoposide 100mg/m² IV D1 to D3

Administration: Furosemide 40mg PO stat Cisplatin in 1 litre 0.9% Sodium Chloride + 20 mmol KCl + 1g MgSO4 IV over 60 minutes Etoposide in Sodium Chloride 0.9% IV over 60 min (See comments for volume) 1 litre 0.9% Sodium Chloride + 40 mmol KCl + 1g MgSO4 IV over 2 hours 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.

Frequency: 3 weekly cycle - Day 1 to Day 3. Total of 6 cycles Assess response after 2 or 3 cycles. Concurrent radiotherapy from cycle 4 onwards. Radiotherapy delivered as 40Gy in 15 fractions over 3 weeks Radiotherapy is given in limited stage disease setting.

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

Regular investigations: FBC D1 (weekly during radiotherapy) LFTs D1 U&Es D1 Mg and Ca (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 - 0.35 mg/ml. (PVC free)

Supportive medication: Prophylactic G-CSF (Pegfilgrastim 6mg s/c on day 4.) should be given on first cycle.

Consider prophylactic antibiotic days 4-13 inclusive on first cycle for patients aged 65 or over, and/or ECOG PS 3 or 4.

**Extravasation:** Non vesicants

**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, ovarian failure/infertility

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 10^9/l or platelets <100 x 10^9/l*

Consider dose reduction (25%) of Etoposide for subsequent cycles if febrile neutropenia occurs

<table>
<thead>
<tr>
<th>Neutrophils x 10^9/l</th>
<th>Platelets x 10^9/l</th>
<th>Cisplatin Dose</th>
<th>Etoposide dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1.5</td>
<td>≥100</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;60ml/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>
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</tbody>
</table>

Subsequent doses based on clinical response

Reason for Update: Hydration, Etoposide concentration limits

Version: 1.1  
Approved by Consultant: A.Montes

Supersedes: All other versions  
Date: 14/08/08

Prepared by: SEestila April08, updated Jan10  
Checked by (Network Pharmacist): J.Turner

Approved by SELCN DTAC Chair: Nic Ketley  
Date: 01/2010
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 nephrotoxic 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>Etoposate dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>26-51 or 60-180</td>
<td>50% dose</td>
<td>&gt;51 or &gt;180 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.
- Apertipant- 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, accessed April 08
SELCN Lung Diagnostic & Treatment Guidelines, July 06
CCO Formulary: CISPET-RT, CISPETOP. Jan 04
BCCA Protocols. LUPE. Revised Oct 05
SWSHCN Protocols. June 07 version
Micromedex review, accessed April 08