Carboplatin / Etoposide (IV D1; PO D2,D3) in Metastatic or Unresectable High Grade Neuroendocrine Carcinoma

**Indication:** Palliative therapy in Metastatic or Unresectable High Grade Neuroendocrine Carcinoma

**Regimen details:**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carboplatin</td>
<td>AUC 6 (if C&amp;G)</td>
<td>IV D1</td>
<td>(see Comments)</td>
</tr>
<tr>
<td>Etoposide</td>
<td>100mg/m²</td>
<td>IV D1</td>
<td></td>
</tr>
<tr>
<td>Etoposide</td>
<td>200mg/m²</td>
<td>PO D2, D3</td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carboplatin</td>
<td>AUC 5 (if EDTA)</td>
<td>IV D1</td>
<td>(see Comments)</td>
</tr>
<tr>
<td>Etoposide</td>
<td>100mg/m²</td>
<td>IV D1</td>
<td></td>
</tr>
<tr>
<td>Etoposide</td>
<td>200mg/m²</td>
<td>PO D2, D3</td>
<td></td>
</tr>
</tbody>
</table>

(Reduced dose or single agent Carboplatin to be considered in elderly patients or in patients with poor performance status)

**Administration:**

Carboplatin in 500mls Glucose 5% IV over 30-60 minutes
Etoposide in Sodium Chloride 0.9% IV over 60 minutes (see comments for volume)
Monitor Etoposide infusion for the first 15 minutes for signs of hypotension
Etoposide capsules: to be swallowed whole on an empty stomach, 30 minutes before or 2 hours after a meal. Daily dose of capsules can be divided in two, if necessary. Available as 50mg and 100mg capsules

**Frequency:** 21 days (Day 1 to Day 3) for 4 cycles

**Extravasation:** Carboplatin and Etoposide: Non-vesicants

**Anti- emetics:** Moderate emetogenic
Follow Local Anti-emetic Policy

**Regular investigations:**

<table>
<thead>
<tr>
<th>Test</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>FBC</td>
<td>D1</td>
</tr>
<tr>
<td>LFTs</td>
<td>D1</td>
</tr>
<tr>
<td>U&amp;Es</td>
<td>D1</td>
</tr>
<tr>
<td>EDTA</td>
<td>Prior to 1st cycle, if necessary (see Comments)</td>
</tr>
<tr>
<td>Baseline CT, CXR</td>
<td>Prior to 1st cycle</td>
</tr>
<tr>
<td>Clinical toxicity assessments</td>
<td>Each cycle</td>
</tr>
</tbody>
</table>

**Comments:**

Carboplatin dose should be calculated using the Calvert formula:
Dose= Target AUC x (25 + GFR)
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. Carboplatin dose is calculated as AUC 5, if EDTA is used.
Monitor trends in serum creatinine between treatments: if > 25% from baseline value, recalculate GFR using the Cockcroft & Gault equation

Etoposide infusion should have maximum concentration of 0.2 – 0.35 mg/ml (PVC free)
Etoposide PO (D2, D3): to be supplied to the patient for oral self-administration together with an information pack and the treatment plan

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Reason for Update: Network Protocol Development
Version: 1.1
Approved by Upper GI Consultant: Paul Ross
Supersedes: All other versions
Date: 18.06.09
Prepared by: Maria Teresa Pacheca-Palomar June ’09
Checked by (Network Pharmacist): Jacky Turner
Approved by SELCN DTAC Chair: Nic Ketley
Date: 24/02/2010
DOSE MODIFICATIONS

Haematological Toxicity

Day 1

WBC < 3.0 x 10^9/ L
or
Neutrophils < 1.5 x 10^9/ L
or
Platelets < 100 x 10^9/ L

Delay for 1 week.
Repeat FBC - If within normal parameters, resume
treatment at full dose. If treatment delayed for subsequent cycles,
consider dose reduction (see below)

Subsequent cycles

If Neutrophils < 1.49 x 10^9/ L ≥ 7 days AND Platelets < 100 x 10^9/ L, OR
Febrile neutropenia is diagnosed,
Consider Etoposide 75% dose and Carboplatin 100% dose

Renal Impairment:
Carboplatin: Contraindicated if CrCl < 20ml/min
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

Hepatic Impairment:
Carboplatin: No dose adjustment required
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>26 – 51</td>
<td>or 60 – 180</td>
<td>Give 50 % dose</td>
</tr>
<tr>
<td>&gt; 51</td>
<td>or &gt; 180</td>
<td>Consultant decision/ Omit</td>
</tr>
</tbody>
</table>

Toxicities:
Myelosuppression; anaemia; thrombocytopenia; leucopenia; peripheral neuropathy (low);
nausea; vomiting; mucositis; diarrhoea; nephrotoxicity; ototoxicity (low); alopecia; taste alteration; chills/fever; ovarian failure; infertility

Anaphylactic reactions have been reported following Etoposide administration

Drug interactions:
Carboplatin :
- Aluminium- containing equipment should not be used during preparation and administration of Carboplatin
- Aminoglycoside antibiotics : increased risk of nephrotoxicity and ototoxicity
- Clozapine : increased risk of agranulocytosis ; avoid concomitant use
- Diuretics : increased risk of nephrotoxicity and ototoxicity
- Nephrotoxic drugs : increased nephrotoxicity ; not recommended
- Phenytoin : reduced absorption of the antiepileptic
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

References:
www.medicines.org.uk
SWSHCN- Approved Network Regimen for SCLC. May 2007
CCO Formulary: ETOPCARBO. Revised October 2007
UCLH-Dosage Adjustment for Cytotoxics in Hepatic Impairment. November 2003
UCLH-Dosage Adjustment for Cytotoxics in Renal Impairment. November 2003
GSTT Guidelines for treating Nausea and Vomiting in adult patients. September 2007
CTCAE v3.0. August 2006