CAP : Cyclophosphamide / Doxorubicin / Cisplatin in Malignant Thymoma

Indication:  
1) First line Induction chemotherapy in Malignant Thymoma  
2) First line Palliative chemotherapy in Malignant Thymoma

Regimen details:  
- Cyclophosphamide 500mg/m² IV D1  
- Doxorubicin 50mg/m² IV D1  
- Cisplatin 50mg/m² IV D1

Administration:  
- Furosemide 40mg orally  
- **Doxorubicin**, IV Bolus injection via a fast-running Sodium Chloride 0.9% infusion over 3 – 10 minutes  
- **Cyclophosphamide** may be administered as a bolus in the side-arm of a fast running saline drip or as a short infusion e.g. in 250ml Sodium Chloride 0.9% over 30 minutes  
- 1litre Sodium Chloride 0.9% + 20mmol KCl + 1g MgSO₄ IV infusion over 60 minutes  
- **Cisplatin**, in 1litre Sodium Chloride 0.9% IV over 2 hours  
- 1litre 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:  
- Induction: Every 21 days, for 6 cycles  
- Palliative: Every 21 days, for 8 cycles

Extravasation:  
- Doxorubicin: Vesicant  
- Cisplatin and Cyclophosphamide: Non-vesicants

Anti-emetics:  
- Highly emetogenic. Follow local Anti-emetic Policy

Regular investigations:  
- FBC D1  
- U&Es D1  
- LFTs D1  
- CXR D1  
- CT scan (disease evaluation) After 3 cycles  
- MUGA scan/ Echocardiogram Prior to 1st cycle (see Comments)

Comments:  
- Maximum cumulative dose Doxorubicin = 450 – 550mg/m²  
- A baseline MUGA scan or Echocardiogram should be performed where the patient is considered at risk of having impaired cardiac function e.g. significant cardiac history, hypertension, obese, smoker, elderly, previous exposure to anthracyclines, previous thoracic radiotherapy. MUGA scan or Echocardiogram should be repeated if there is suspicion of cardiac toxicity at any point during treatment, or if cumulative anthracycline dose approaches maximum
Hydration / fluid balance - 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 - 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

DOSE MODIFICATIONS
Haematological Toxicity

<table>
<thead>
<tr>
<th>Neutrophils</th>
<th>Platelets</th>
<th>Cyclophosphamide and Doxorubicin Doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1.5 x 10⁹/L and ≥ 100 x 10⁹/L</td>
<td>Give 100%</td>
<td></td>
</tr>
<tr>
<td>1.0 – 1.4 x 10⁹/L or 75 – 99 x 10⁹/L</td>
<td>Give 50% dose</td>
<td></td>
</tr>
<tr>
<td>&lt; 1.0 x 10⁹/L or &lt; 75 x 10⁹/L</td>
<td>Delay for 1 week</td>
<td></td>
</tr>
</tbody>
</table>

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 25% from baseline value, re-calculate GFR using the Cockcroft & Gault equation

Doxorubicin: Dose reduction in severe renal impairment (GFR < 10 ml/min) should be discussed with Consultant

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>
Reason for Update: Network Protocol Development

Cyclophosphamide: Patients should be initiated with full-dose treatment unless serum creatinine > 120 μmol/l. If serum creatinine > 120 μmol/l, dose adjustments for Cyclophosphamide should be made using Cockcroft and Gault and the guidelines below.

<table>
<thead>
<tr>
<th>CrCl (ml/min)</th>
<th>Cyclophosphamide Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 50</td>
<td>Give 100%</td>
</tr>
<tr>
<td>10 – 50</td>
<td>Give 75%</td>
</tr>
<tr>
<td>&lt; 10</td>
<td>Give 50%</td>
</tr>
</tbody>
</table>

Hepatic Impairment: Cisplatin: No dose reduction necessary.

Cyclophosphamide is not recommended in patients with a bilirubin > 17 μmol/L or AST/ALT more than 2 – 3 x upper normal limit, however, exposure to active metabolites may not be increased, suggesting that dose reduction may not be necessary. Decision should be discussed with the Consultant.

Doxorubicin dose should be adjusted as follows:

<table>
<thead>
<tr>
<th>Bilirubin (μmol/L)</th>
<th>Doxorubicin Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 20</td>
<td>Give 100%</td>
</tr>
<tr>
<td>20 – 50</td>
<td>Give 50%</td>
</tr>
<tr>
<td>51 – 85</td>
<td>Give 25%</td>
</tr>
<tr>
<td>&gt; 85</td>
<td>Omit</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>AST/ALT (units)</th>
<th>Doxorubicin Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 – 3 x normal</td>
<td>Give 75%</td>
</tr>
</tbody>
</table>

DOSE MODIFICATIONS FOR OTHER TOXICITIES AS APPROPRIATE

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>Discontinue therapy</td>
</tr>
<tr>
<td>4</td>
<td>Disabling</td>
<td>Disabling</td>
<td>Discontinue therapy</td>
</tr>
</tbody>
</table>

Version: 1  Approved by Lung Consultant: Rohit Lal
Supersedes: All other versions  Date: 21.04.10
Prepared by: Maria Teresa Pacheca-Palomar  April’10
Checked by (Network Pharmacist): Jacky Turner
Approved by SELCN DTAC Chair: Nic Ketley  Date: 26.04.10

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Toxicities: Myelosuppression; fatigue; nausea; vomiting; constipation; diarrhoea; mucositis; nephrotoxicity; neuropathy / ototoxicity; cardiotoxicity; haemorrhagic cystitis; taste alteration; electrolyte disturbances; allergic reactions; alopecia

Drug interactions: Cyclophosphamide and Doxorubicin:
- Clozapine: increased risk of agranulocytosis, avoid concomitant use
- Digoxin tablets: reduced absorption (resolved by giving the digoxin in liquid)
- Phenytoin: reduced absorption of the antiepileptic
- Warfarin: the anticoagulant effect is increased

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 (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

Doxorubicin:
- Ciclosporin (high dose) increase Doxorubicin serum levels and myelotoxicity
- Concomitant use of other cardioactive compounds e.g. calcium channel blockers require monitoring of cardiac function throughout treatment
- Quinolones: antimicrobial effect of quinolones decreased

Cyclophosphamide:
- Allopurinol: can increase the incidence of serious bone marrow depression
- Amiodarone: increased risk of pulmonary fibrosis; avoid combination if possible
- Grapefruit juice: decreased or delayed activation of Cyclophosphamide
- Avoid grapefruit juice for 48 hours before and on day of dose
- Indapamide: prolonged leucopenia is possible
- Itraconazole: might increase Cyclophosphamide side effects e.g. haemorrhagic cystitis, pigmentation of palms, nails and soles etc...

References: www.medicines.org.uk
Loehrer PJ et al. JCO (1994); Vol 12, No 6: 1164 - 1168
BC Cancer Agency Protocol Summary ULUOTPC. April 2009