CAV : Cyclophosphamide / Doxorubicin / Vincristine in Small Cell Lung Cancer

Indication: Second-line chemotherapy for limited and extensive Small Cell Lung Cancer (SCLC)

Regimen details:

- Cyclophosphamide 600mg/m² IV D1
- Doxorubicin 50mg/m² IV D1
- Vincristine 2mg IV D1

May consider Vincristine 1.5mg if patient > 70

Administration:

- Vincristine in 50mls Sodium Chloride 0.9% IV infusion over 5 – 10 minutes
- Doxorubicin injected into the side arm of a fast-running saline drip 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 100ml Sodium Chloride 0.9% over 30 minutes

Frequency: 21 days, for 4 – 6 cycles

Extravasation:

- Vincristine and Doxorubicin: Vesicants
- Cyclophosphamide: Non-vesicant

Anti-emetics:

- Vincristine: minimal emetogenic
- Doxorubicin and Cyclophosphamide: moderate emetogenics

Supportive medication:

- Prophylactic oral antibiotic, starting on Day 8, to cover the nadir, and growth factor support should be used for the first cycle of treatment, following the Antibiotic Trust Guidelines and the local guidelines for the use of Colony Stimulating Factors to manage Neutropenia, respectively

Regular investigations:

- FBC D1
- LFTs D1
- U&Es D1
- CrCl D1
- CXR Every cycle
- MUGA scan Prior to 1st cycle (see Comments)

Comments:

- Maximum cumulative dose Doxorubicin = 450 – 550mg/m²
- A baseline MUGA scan 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 should be repeated if there is suspicion of cardiac toxicity at any point during treatment, or if cumulative anthracycline dose approaches maximum
DOSE MODIFICATIONS

Haematological Toxicity

Day 1

- WBC < 3.0 x 10^9/L
  - Delay for 1 week.
  - Repeat FBC - If within normal parameters, resume treatment with 100% doses
- Neutrophils < 1.5 x 10^9/L
  - or
- Platelets < 100 x 10^9/L

Subsequent cycles

- Doxorubicin and Cyclophosphamide doses should be reduced to 75% doses if:
  - Neutrophils < 0.5 x 10^9/L for ≥ 7 days or febrile neutropenia is diagnosed OR
  - Neutrophils < 1.0 – 0.5 x 10^9/L lasting beyond day 21 of the treatment cycle OR
  - Platelets < 25 x 10^9/L

- Do not escalate for subsequent cycles

Renal Impairment:

- Vincristine: No dose reduction necessary
- Doxorubicin: Dose reduction in severe renal impairment (GFR < 10 ml/min) should be discussed with the Consultant
- 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:

- 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 and Vincristine doses should be adjusted as follows:

<table>
<thead>
<tr>
<th>Bilirubin (µmol/L)</th>
<th>Doxorubicin Dose</th>
</tr>
</thead>
<tbody>
<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>

<table>
<thead>
<tr>
<th>Bilirubin (µmol/L)</th>
<th>AST/ ALT (units)</th>
<th>Vincristine Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>26-51</td>
<td>or</td>
<td>Give 50%</td>
</tr>
<tr>
<td>&gt; 51</td>
<td>and</td>
<td>normal</td>
</tr>
<tr>
<td>&gt; 51</td>
<td>and</td>
<td>&gt; 180</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Omit</td>
</tr>
</tbody>
</table>
DOSE MODIFICATIONS FOR OTHER TOXICITIES AS APPROPRIATE

Vincristine: Elderly patients may be more susceptible to the neurotoxic effects of Vincristine. In the event of neurotoxicity, consider dose reduction of Vincristine as follows:

<table>
<thead>
<tr>
<th>Neurotoxicity symptoms</th>
<th>Vincristine Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paresthesia (including tingling) but not interfering with function</td>
<td>Give 100%</td>
</tr>
<tr>
<td>Paresthesia interfering with function, but not interfering with ADL</td>
<td>Give 75%</td>
</tr>
<tr>
<td>Paraesthesia interfering with ADL</td>
<td>Omit Vincristine until toxicity resolved</td>
</tr>
<tr>
<td>Disabling</td>
<td>Omit Vincristine until toxicity resolved</td>
</tr>
</tbody>
</table>

Toxicities: Neutropenia; leukopenia; anaemia; thrombocytopenia; infection; peripheral neuropathy; cardiotoxicity; haemorrhagic cystitis; nausea; vomiting; diarrhoea; fatigue; alopecia; stomatitis; mucositis; discoloured urine; infertility; amenorrhoea; oligospermia; azoospermia; hyperuricaemia

Drug interactions:
- Cyclophosphamide, Doxorubicin and Vincristine:
  - Phenytoin: reduced blood levels of the anticonvulsant and increased seizure activity
  - Warfarin: the anticoagulant effect is increased

Vincristine:
- Itraconazole is contraindicated with Vincristine, causing an earlier onset and/or an increased severity of neuromuscular side-effects e.g. neuritic pain, sensory loss, paraesthesia, difficulty in walking etc...
- Allopurinol, pyridoxine and isoniazid may increase the incidence of bone marrow depression
- Asparaginase: should be given 12 to 24 hours after Vincristine
- Drugs acting on the peripheral nervous system can increase Vincristine neurotoxicity

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

Cyclophosphamide:
- Itraconazole: Cyclophosphamide side effects e.g. haemorrhagic cystitis, pigmentation of palms, nails and soles etc.. are increased
References:

www.medicines.org.uk
Von Pawel et al. JCO 17:2;658-667
SWSHCN- Network Approved Regimen for Lung Cancer. May 2008
GSTT Guidelines for treating nausea and vomiting in adult patients. September 2007
UCLH- Dosage Adjustment for Cytotoxics in Renal Impairment. November 2003
UCLH- Dosage Adjustment for Cytotoxics in Hepatic Impairment. November 2003
CTCAE v 3.0. August 2006