B6.8 CBOP/BEP

B6.8.1 Indication
- Radical therapy for poor prognosis metastatic non-seminomatous germ cell cancers.

B6.8.2 Pre treatment evaluation
- Multi-disciplinary review and histological confirmation
- Investigations should include CT scan of chest, abdomen and pelvis
- Record WHO performance status, current height, weight and surface area
- FBC, U&Es (including Magnesium and Calcium), Serum Creatinine, LFTs, AFP, HCG, LDH
- Consider formal measurement of creatinine clearance in patients with low surface area using either 24-hour urine collection or EDTA measurements.
- Creatinine clearance should ideally be >60 mls/min (refer to renal dose modification table)
- Document evaluable disease where appropriate
- Consider auditory assessment and pulmonary function tests
- Sperm storage must be discussed/organised before treatment starts
- Document evaluable disease
- Give adequate verbal and written information for patients and relatives concerning patient’s disease, treatment strategy and side effects/mortality risk
- If appropriate, discuss potential risk of infertility/early menopause with patient and relatives
- Obtain written consent from patient or guardian
# B6.8.3 Drug Regimen

CBOP administered over first 6 weeks followed by 3 cycles of 5 day BEP administered every 21 days

**CBOP**

<table>
<thead>
<tr>
<th>Days</th>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1, 2 &amp; 15, 16</td>
<td>Cisplatin †</td>
<td>50mg/m²</td>
<td>IV</td>
<td>IV infusion in 1000ml Sodium Chloride 0.9% over 2 - 6 Hours with pre and post hydration</td>
</tr>
<tr>
<td>8 &amp; 22</td>
<td>Cisplatin †</td>
<td>40mg/m²</td>
<td>IV</td>
<td>IV infusion in 1000ml Sodium Chloride 0.9% over 1 - 6 Hours with pre and post hydration</td>
</tr>
<tr>
<td>8 &amp; 22</td>
<td>Carboplatin</td>
<td>AUC 3</td>
<td>IV</td>
<td>IV infusion in 500ml Glucose 5% over 60 minutes †††</td>
</tr>
<tr>
<td>1, 8, 15, 22, 29, 36</td>
<td>Vincristine</td>
<td>2mg</td>
<td>IV</td>
<td>Intravenous infusion in 50ml sodium chloride 0.9% over 10 minutes, as per national guidance. Nurse to remain with patient throughout infusion Sodium Chloride 0.9%</td>
</tr>
<tr>
<td>1, 8</td>
<td>Bleomycin ††</td>
<td>15,000iu</td>
<td>IV</td>
<td>Bolus injection over 3 – 5 minutes</td>
</tr>
<tr>
<td>8-12 22-26</td>
<td>Bleomycin ††</td>
<td>75,000iu</td>
<td>IV</td>
<td>IV continuous infusion in 1000ml Sodium Chloride 0.9% over 5 days (i.e. 15,000iu/day)</td>
</tr>
</tbody>
</table>

† Refer to ASWCS Individual Drug Guidelines for specific recommendations when administering Cisplatin (Section A3.2)

†† Give 100mg Hydrocortisone IV 30 minutes prior to Bleomycin in order to prevent Bleomycin-induced rigors. Chlorphenamine 10mg IV +/- Paracetamol 1g po can be added to the regimen if hypersensitivity reactions occur

††† Calculate Carboplatin dose using Calvert equation:

\[
\text{Carboplatin dose (mg)} = \frac{\text{AUC}}{\text{GFR} + 25}
\]
BEP (5 day)

<table>
<thead>
<tr>
<th>Days</th>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 - 5</td>
<td>Cisplatin †</td>
<td>20mg/m²</td>
<td>IV</td>
<td>IV infusion in 500-1000ml Sodium Chloride 0.9% over 2 – 6 Hours with pre and post hydration</td>
</tr>
<tr>
<td></td>
<td>Etoposide</td>
<td>100mg/m²</td>
<td>IV</td>
<td>IV infusion in 1000ml Sodium Chloride 0.9% over 60 minutes</td>
</tr>
<tr>
<td>2, 9 &amp; 16</td>
<td>Bleomycin † †</td>
<td>15,000 IU</td>
<td>IV</td>
<td>IV infusion in 100ml Sodium Chloride 0.9% over 30 minutes</td>
</tr>
</tbody>
</table>

† Refer to ASWCS Individual Drug Guidelines for specific recommendations when administering Cisplatin (Section A3.2)

†† Give 100mg Hydrocortisone IV 30 minutes prior to Bleomycin in order to prevent Bleomycin-induced rigors. Chlorphenamine 10mg IV +/- Paracetamol 1g po can be added to the regimen if hypersensitivity reactions occur. Dose limited to 15,000iu to reduce total cumulative dose and thus limit pulmonary toxicity.

B6.8.4 Additional Modifications

- Germ-cell tumours can be very sensitive to cytotoxic chemotherapy, resulting in a massive tumour lysis at the start of treatment. Prophylactic Allopurinol 300mg po once a day (reduced in renal impairment) should be considered to prevent this starting the day before chemotherapy and continued for as long as a significant bulk of chemotherapy-sensitive tumour remains (usually 28 days)
- Monitor the fluid balance/body weight on a daily basis. If the patient has gained more than 1.5L/kg during chemotherapy, extra diuresis should be given.
- NOTE: For statutory holidays and weekends: The standard is to give treatments on 5 consecutive days and not 5 out of 7 days. For the occasional patient, 125% daily for 4 consecutive days may be considered.

B6.8.5 Dose Modifications

- Dose adjustments within a cycle of BEP will be made following the guidelines shown in the following guidelines based on weekly white blood cell (WBC), absolute neutrophils count (ANC), platelet counts and clinical assessment of non-haematological toxicity.

B6.8.5.1 Haematological

- CBOP: If at the start of any treatment cycle the WBC <0.8 x 10⁹/l, ANC <0.5 x 10⁹/l or PLT <80 x 10⁹/l delay treatment for 3 days. FBC should be repeated every 3 days until these levels are reached then use the table below for dose adjustments.
ASWCS Haematology Chemotherapy Protocols

- **BEP**: If at the start of any treatment cycle the WBC <1.5 x 10⁹/l, ANC <0.5 x 10⁹/l or PLT <50 x 10⁹/l delay treatment for 3 days. FBC should be repeated every 3 days until these levels are reached then use the table below for dose adjustments:

<table>
<thead>
<tr>
<th>Platelet Count x 10⁹/L</th>
<th>WBC x 10⁹/L</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&gt;2.1</td>
</tr>
<tr>
<td></td>
<td>&gt;100</td>
</tr>
<tr>
<td>Etoposide</td>
<td>100%</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>100%</td>
</tr>
<tr>
<td>Etoposide</td>
<td>50%</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>75%</td>
</tr>
<tr>
<td>Etoposide</td>
<td>delay 3 days</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>delay 3 days</td>
</tr>
</tbody>
</table>

- As Bleomycin only causes minimally myelosuppression, no dose modification is necessary **except** if the patient has febrile neutropenia, when treatment should be delayed until count recovery.

- No dose modifications should be made based on the nadir counts from the previous cycle. Each cycle should be assessed independently (i.e. dose modifications should **not** be continued through subsequent cycles in the absence of significant myelosuppression).

- In the event of neutropenic sepsis, no dose reduction is made provided full haematological recovery has occurred by day 21. The use of GCSF should be considered in future cycles.

- However in the case of complicated neutropenia, dose modifications should be maintained for all remaining courses:
  - i.e. Grade 3 & 4 infections despite secondary GCSF prophylaxis
  - or neutropenia Grade 4 lasting more than 7 days despite GCSF
  - or Grade 4 thrombocytopenia lasting more than 3 days or requiring platelets
  - Any grade 4 neutropenia with a single oral temp >38.5°C should result in administration of prophylactic antibiotics in all subsequent courses (e.g. Ciprofloxacin 250 mg bd)

### B6.8.5.2 Renal Function

- **Cisplatin**: Full dose Cisplatin is given unless creatinine clearance falls below 40 ml/min. If clearance falls below 40 ml/min on subsequent testing Cisplatin **should be** discontinued. If renal function recovers, Cisplatin should be re-started at 75% of prior dose. Full dose Cisplatin may be resumed if recovery of renal function to initial level occurs. Substitution with Carboplatin is possible although should be discussed with consultant.

- **Carboplatin**: * Do not use calculated methods such as Cockcroft & Gault for GFR measurement in patients with a low body surface area (i.e. <1.4m²) or in patients with a calculated renal function of <30ml/min. Instead, calculate GFR using either 24-hour urine collection or EDTA measurements ONLY. Carboplatin is contraindicated in patients with a GFR <20ml/min.
ASWCS Haematology Chemotherapy Protocols

- **Etoposide**: If CrCl \(\geq 60\text{ml/min}\) then give 100% dose
  - If CrCl 46-60ml/min then give 85% dose
  - If CrCl 30-45ml/min then give 80% dose
  - If CrCl <30ml/min then give 75% dose

- **Bleomycin**: If CrCl \(\geq 50\text{ml/min}\) then give 100% dose
  - If CrCl 10-50ml/min then give 75% dose
  - If CrCl <10ml/min then give 75% dose

### B6.8.5.3 Hepatic Function

- **Cisplatin**: No dose modifications for hepatic impairment
- **Carboplatin**: No dose modifications for hepatic impairment
- **Etoposide**: If Bilirubin 26-51\(\mu\text{mol/L}\) or AST 60-180iu/L give 50%
  - If Bilirubin >51\(\mu\text{mol/L}\) or AST >180iu/L then the decision to treat should be discussed with the consultant

- **Bleomycin**: Little information: discuss with consultant

### B6.8.5.4 Other Non-Haematological Dose Modifications

- **Bleomycin**: Limiting the total cumulative Bleomycin dose to 270 units should decrease the risk of pulmonary toxicity but clinical assessment before each cycle can help identify signs of lung disease at an early stage.

### B6.8.6 Antiemetics/supportive therapy

- This regimen has moderate to severe emetic potential - refer to local protocol

### B6.8.7 Cycle frequency

- CBOP administered over first 6 weeks followed by 3 cycles of 5 day BEP administered every 21 days. Total schedule = 15 weeks

### B6.8.8 Adverse effects

- Nausea/vomiting
- Myelosuppression and risk of sepsis and thrombocytopenia
- Constipation and/or diarrhoea
- Alopecia
- Peripheral neuropathy & ototoxicity including tinnitus
- Encephalopathy
- Caution with extravasation due to vesicant drugs
- Nephrotoxicity
- Ototoxicity
- Stomatitis & Mucositis
ASWCS Haematology Chemotherapy Protocols

- Lung fibrosis
- Raynaud’s Disease
- Hypotension
- Rigors
- Infertility
- Long term risks of second malignancy and CVS disease
- Fatigue

**B6.8.9 Investigations Prior to Subsequent Cycles**

- Before each course check:
  - FBC
  - U&Es (including albumin & magnesium)
  - Serum Creatinine and consider formal measurement of creatinine clearance in patients with low surface area using either 24-hour urine collection or EDTA measurements. Ensure that calculated creatinine clearance >60mls/min (refer to renal dose modification table)
  - LFTs (i.e. ALT (or AST), AlkPhos, Bilirubin)
  - AFP, HCG, LDH (take sample but it is not necessary to wait for result before proceeding with treatment)
  - Clinical toxicity assessment should be undertaken (including stomatitis, neurotoxicity & lung function (which should include a careful survey of respiratory symptoms, chest auscultation and chest x-ray). Pulmonary function tests should be repeated in suspect cases of pulmonary toxicity, particularly if more than 270iu of Bleomycin treatment is given (i.e. during the 2nd and 3rd cycles of BEP)
B6.8.10 References


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<table>
<thead>
<tr>
<th>Written By: Dr J Braybrooke, BHOC</th>
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<tbody>
<tr>
<td>Updated for vinca alkaloid administration only 30/01/2009</td>
</tr>
<tr>
<td>Update written by Becky Bagnall, Pharmacist BHOC</td>
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<tr>
<td>Update authorised by Jeremy Braybrooke, Chairman ASWCS D+T committee</td>
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<table>
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<tr>
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<tbody>
<tr>
<td>Chairman of ASWCS Network Pharmacist Group</td>
</tr>
<tr>
<td>Name: Jarrod Dunn</td>
</tr>
<tr>
<td>Signature: Dunn</td>
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