Bleomycin, Etoposide and Cisplatin (BEP) Therapy

INDICATIONS FOR USE:

<table>
<thead>
<tr>
<th>INDICATION</th>
<th>ICD10</th>
<th>Protocol Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjuvant treatment of high risk (vascular invasion carcinoma) stage 1 nonseminoma germ cell tumour</td>
<td>C62</td>
<td>00300a</td>
</tr>
<tr>
<td>Metastatic germ cell tumours of the testis</td>
<td>C62</td>
<td>00300b</td>
</tr>
<tr>
<td>Advanced stage or metastatic germ cell tumours (dysgerminoma) of the ovaries</td>
<td>C56</td>
<td>00300c</td>
</tr>
<tr>
<td>Extra-gonadal germ cell tumours</td>
<td>C56/C62</td>
<td>00300d</td>
</tr>
</tbody>
</table>

ELIGIBILITY:
- Indications as above
- ECOG status 0-3

EXCLUSIONS:
- Hypersensitivity to bleomycin, etoposide, cisplatin or any of the excipients.
- Bleomycin is contraindicated in patients with acute pulmonary infection or chest X rays suggesting diffuse fibrotic changes or greatly reduced lung function
- Cisplatin
  - Pre existing neuropathies ≥ grade 2
  - Creatinine clearance < 40 mL/min
  - Significant hearing impairment/tinnitus
- Severe liver impairment (etoposide)

TESTS:
Baseline tests:
- FBC, U&Es, LFTs, creatinine.
- Pulmonary function tests (PFTs) and Chest X-ray prior to bleomycin
- Consider sperm banking for appropriate patients prior to initiation of therapy

Regular tests:
- FBC weekly during treatment
- U&Es, LFTs, creatinine prior to each treatment cycle

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This information is valid only on the day of printing, for any updates please check [www.hse.ie/NCCPchemoprotocols](http://www.hse.ie/NCCPchemoprotocols).
Chest X-ray prior to each cycle  
PFTs as clinically indicated

**Disease monitoring/assessment:**  
Disease monitoring/assessment should be in line with the patient’s treatment plan and any other test/s as directed by the supervising Consultant.

**TREATMENT:**  
The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patient’s individual clinical circumstances.  
Treatment with etoposide and cisplatin is administered on days 1-5, and treatment with bleomycin is administered on days 1, 8 and 15 of a 21 day cycle.  
For good risk patients - 3 cycles are administered,  
For intermediate to poor risk patients - 4 cycles are administered  
Facilities to treat anaphylaxis MUST be present when the chemotherapy is administered.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Diluent and Rate</th>
<th>Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleomycin</td>
<td>(^a) 30,000 IU (30mg)</td>
<td>IV Bolus Or IM</td>
<td></td>
<td>1, 8 and 15</td>
</tr>
<tr>
<td>Etoposide</td>
<td>100mg/m(^2)</td>
<td>IV infusion</td>
<td>1000ml 0.9% NaCl over 30-120 minutes(^b)</td>
<td>1-5</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>20mg/m(^2)</td>
<td>IV infusion</td>
<td>500 to 1000ml 0.9% NaCl over 1 hour (Pre hydration therapy required)(^d)</td>
<td>1-5</td>
</tr>
</tbody>
</table>

Bleomycin dosing may be referred to in IU or in mg. 1,000IU = 1mg.

\(^a\) The total cumulative dose of bleomycin should NOT exceed 400,000 international units (400mg). The risk of pulmonary toxicity increases beyond a cumulative dose of 300,000 international units (300mg).

\(^b\) For IM injection dose is dissolved in up to 5ml 0.9% NaCl. If pain occurs at the site of injection a 1% solution of lignocaine may be used as a solvent (6)

\(^c\) Hypotension following rapid IV administration has been reported. Longer infusion times may be required based on the patient’s tolerance

\(^d\) Prehydration therapy required prior to Cisplatin  
See local hospital policy recommendations.  
Suggested prehydration for cisplatin therapy:

**NCCP Protocol: BEP Therapy**  
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Review: 08/04/2016  
Version number: 1

**Tumour Group: Genitourinary/Gynaecology**  
NCCP Protocol Code: 00300  
IHS Contributor: Dr Maccon Keane  
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DOSE MODIFICATIONS

- Any dose modification should be discussed with a Consultant.

Haematological:

- Delay and dose reductions are not recommended as the efficacy of this treatment may be greatly compromised.
- All delays to treatment must be approved by prescribing consultant.
- Prophylactic use of G-CSF is not recommended.
- G-CSF is indicated in patients receiving their second or subsequent cycle of BEP who have had an episode of neutropenic fever or who have not recovered their neutrophil count by Day 5.

Renal Impairment:

- **Bleomycin**

  **Table 1: Dose modification of BLEOMYCIN in renal impairment**

<table>
<thead>
<tr>
<th>Creatinine Clearance (ml/min)</th>
<th>Dose of Bleomycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;50</td>
<td>100%</td>
</tr>
<tr>
<td>10-50</td>
<td>75%</td>
</tr>
<tr>
<td>&lt;10</td>
<td>50%</td>
</tr>
</tbody>
</table>

- **Etoposide**

  **Table 2: Dose modification of ETOPOSIDE in renal impairment**

<table>
<thead>
<tr>
<th>Creatinine Clearance (ml/min)</th>
<th>Dose of Etoposide</th>
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<tr>
<td>&gt;50</td>
<td>100%</td>
</tr>
<tr>
<td>15-50</td>
<td>75%</td>
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Subsequent dosing should be based on patient tolerance and clinical effect. Data are not available in patients with creatinine clearance < 15ml/min and further dose reductions should be considered in these patients.

Administer 10mmol magnesium sulphate (MgSO₄) in 1000 mL sodium chloride 0.9% over 60 minutes. 
Administer cisplatin as described above.
**NCCP Chemotherapy Protocol**

- **Cisplatin:**
  
  Table 3: Dose modification of CISPLATIN in renal impairment

<table>
<thead>
<tr>
<th>GFR (ml/min)</th>
<th>Dose of Cisplatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 60</td>
<td>100%</td>
</tr>
<tr>
<td>*45-59</td>
<td>75%</td>
</tr>
<tr>
<td>&lt;45</td>
<td>Hold cisplatin or delay with additional IV fluids</td>
</tr>
</tbody>
</table>

*Due to the curative intent of this chemotherapy regimen, in cases where Cr CI falls between 45-59ml/min it may be appropriate to maintain dose of cisplatin but with extra hydration, longer infusion time and daily Creatinine measurements at the discretion of the prescribing consultant.

**Hepatic Impairment:**

- **Bleomycin:** No dose recommendations available in SmPC, clinical decision
- **Cisplatin:** No dose reduction necessary
- **Etoposide:**

Table 4: Dose modification of ETOPOSIDE based on hepatic function

<table>
<thead>
<tr>
<th>Bilirubin (micromol/L)</th>
<th>AST (Units/L)</th>
<th>Dose Etoposide</th>
</tr>
</thead>
<tbody>
<tr>
<td>26-51 or 60-180</td>
<td>50%</td>
<td></td>
</tr>
<tr>
<td>&gt;51 or &gt;180</td>
<td>Clinical decision</td>
<td></td>
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**Bleomycin Induced Lung Toxicity:**

- Bleomycin can be associated with the development of life-threatening pulmonary toxicity.
- Bleomycin should be discontinued in patients demonstrating clinical or radiographic evidence of pulmonary injury or significant deterioration of pulmonary diffusion capacity.
- Do not reintroduce bleomycin to patients with any bleomycin-induced lung injury.

**SUPPORTIVE CARE:**

**EMETOGENIC POTENTIAL:**

Days 1-5 High

Days 8, 15 Minimal (Refer to local policy).

**PREMEDICATIONS:**

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Hydration prior to cisplatin administration (Reference local policy or see recommendations above).

TAKE HOME MEDICATIONS:
None required

OTHER SUPPORTIVE CARE:
No specific recommendations

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS
This medicinal product is subject to additional monitoring. Healthcare professionals are asked to report any suspected adverse reactions.
The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

- **Pulmonary toxicity**: Bleomycin: may cause severe and life threatening pulmonary toxicity. Pulmonary toxicity of bleomycin is both dose-related and age-related. It may also occur when lower doses are administered, especially in elderly patients, patients with reduced kidney function, pre-existing lung disease, previous or concurrent radiotherapy to the chest and in patients who need administration of oxygen. It is significantly enhanced by thoracic radiation and by hyperoxia used during surgical anaesthesia.

- **Hypersensitivity**: Hypersensitivity reactions have been reported with etoposide and cisplatin. Monitor infusion of etoposide for the first 15 minutes for signs of hypotension.

- **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated appropriately. Avoid aminoglycoside antibiotics.

- **Renal Toxicity**: Nephrotoxicity is common with cisplatin. Strongly encourage oral hydration. If oral hydration is not possible (e.g. excessive nausea), IV hydration is indicated. Avoid nephrotoxic drugs such as aminoglycoside antibiotics where possible. Where treatment with nephrotoxic drugs must be used, monitor renal function.

- **Ototoxicity and sensory neural damage**: These are associated with cisplatin therapy. They should be assessed by history prior to each cycle.

DRUG INTERACTIONS:

- Bleomycin causes sensitization of lung tissue to oxygen. If oxygen is required the use of low concentration (e.g. 25%) is recommended. Fluid replacement should be

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carefully monitored with emphasis on administration of colloid rather than crystalloid to avoid interstitial pulmonary oedema.

- Cisplatin may potentiate the nephrotoxic and ototoxic effects of loop diuretics and aminoglycosides so concurrent use should be avoided.
- Concomitant cisplatin therapy is associated with reduced total body clearance of etoposide.
- CYP3A4 inducers may increase the clearance of etoposide.
- CYP3A4 and p-gp inhibitors may decrease the clearance of etoposide
- Current drug interaction databases should be consulted for more information.

**ATC CODE:**
Bleomycin - L01DC01
Etoposide - L01CB01
Cisplatin - L01XA01

**REIMBURSEMENT CATEGORY:**
Bleomycin, etoposide and cisplatin are funded through local hospital budgets (January 2016).

**PRESCRIPTIVE AUTHORITY:**
Consultant medical oncologist

**REFERENCES:**
4. Nichols et al. Randomized comparison of cisplatin and etoposide and either bleomycin or ifosfamide in treatment of advanced disseminated germ cell tumors: an Eastern Cooperative Oncology Group, Southwest Oncology Group,

<table>
<thead>
<tr>
<th>Version</th>
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<th>Amendment</th>
<th>Approved By</th>
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<tbody>
<tr>
<td>1</td>
<td>8/04/2016</td>
<td>Initial Draft</td>
<td>Dr Maccon Keane</td>
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<tr>
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<td></td>
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Comments and feedback welcome at oncologydrugs@cancercontrol.ie.