BEP: Bleomycin / Etoposide / Cisplatin in Germ Cell Tumours
(5-day regimen)

Indication:
1) First line therapy for Germ Cell Tumours (curative intent)
2) First line therapy for Ovarian Granulosa Cell Tumours (all intents)

Regimen details:
- Etoposide 100mg/m² IV D1-D5
- Cisplatin 20mg/m² IV D1-D5
- Bleomycin 30,000 IU IV D1, D8, D15

Administration:

Days 1 - 5
- Furosemide 40mg orally
- **Etoposide** in Sodium Chloride 0.9% IV over 60 minutes (see below for volume)
- Etoposide infusion should have maximum concentration of 0.2 – 0.35 mg/ml (PVC free)
- Monitor Etoposide infusion for the first 15 minutes for signs of hypotension
- **Cisplatin** IV infusion over 1 hour
- 1litre Sodium Chloride 0.9% + 20mmol KCl + 1g MgSO₄ IV infusion over 1 hour
- Then either 500ml Sodium Chloride 0.9% IV 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

Days 1, 8 and 15
- **Bleomycin** in 100ml Sodium Chloride 0.9% IV over 15 minutes

Day 6
- Pegfilgrastim 6mg given subcutaneously

Premedication:
- Hydrocortisone 100mg IV in 50 - 100m l Sodium Chloride over 10-15 minutes (prior to Bleomycin, to prevent rigors)

Frequency:
- Every 21 days, maximum 4 cycles

Extravasation:
- Bleomycin, Etoposide and Cisplatin are Non-vesicants

Anti-emetics:
- D1-D5: Moderate to severe emetogenicity. Uncontrolled vomiting may exacerbate Cisplatin-induced fluid and electrolyte imbalance. Follow Local Anti-emetic Policy
- D8 & D15: Mild emetogenicity. Follow Local Anti-emetic Policy

Supportive medication:
- Primary Prophylactic Growth Factor support should be used starting at least 24 hours post chemotherapy given with each cycle of chemotherapy, following the local Guidelines for the Use of Colony Stimulating Factors to Manage Neutropenia e.g. Pegfilgrastim on day 6

Regular investigations:
- FBC D1, D8, D15
- LFTs D1
- U&Es D1 (Creatinine D8, D15)
- Mg²⁺ and Ca²⁺ D1
- AFP, HCG, LDH Prior to each cycle
- CXR Prior to each cycle
- Auscultation of chest Prior to each dose of Bleomycin

Reason for Update: Network Protocol Development
Approved by Gynaecology Consultant: Ana Montes
Version: 3.1
Approved by Urology Consultant: Hartmut Kristeleit
Supersedes: All other versions
Date: 30.04.10
Prepared by: Maria Teresa Pacheca-Palomar April’10
Checked by (Network Pharmacist):
Approved by SELCN DTAC Chair: Janine Mansi
Date: 19.05.10
Pulmonary function tests Prior to 1st cycle. Repeat only if clinically indicated
EDTA Prior to 1st cycle, if clinically indicated
Audiogram Prior to 1st cycle, if clinically indicated
Ca 125 Prior to each cycle for female patients

Comments: Lung fibrosis – Bleomycin

Bleomycin may cause severe and life-threatening pulmonary toxicity. Different factors, such as age (>40 years), drug dose, poor renal function, advanced disease, smoking history, concomitant use of oxygen or radiation therapy can influence the risk of developing pulmonary toxicity. To decrease the risk of pulmonary toxicity use maximum cumulative dose of Bleomycin according to table below:

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Maximum Bleomycin cumulative dose (IU)</th>
</tr>
</thead>
<tbody>
<tr>
<td>60 and over</td>
<td>Refer to Bleomycin Summary of Product Characteristics</td>
</tr>
<tr>
<td>Under 60</td>
<td>360,000</td>
</tr>
</tbody>
</table>

Patients undergoing treatment with Bleomycin should be monitored with:
- Chest auscultation prior to each cycle
- Chest X Ray
- Lung function test including DLCO

If there is any pre-existing lung condition, or DLCO is below 50% of predicted, discuss with Consultant.

If during treatment, pulmonary toxicity occurs (dyspnoea, radiological pneumonitis, decrease in FVC or DLCO < 30% of pre-treatment value), Bleomycin should be discontinued.

Oxygen may precipitate or aggravate Bleomycin pulmonary toxicity. Oxygen concentration must not exceed 30-40% unless absolutely necessary, therefore, it is recommended to use room air for lung function tests. Scuba diving is not recommended.

Acute hypersensitivity reactions – Bleomycin

Bleomycin has been associated with acute hypersensitivity reactions in 1% of patients with lymphoma and < 0.5% patients with solid tumours. The reactions are characterized by high grade fever, chills, hypotension, and occasionally collapse and death.

Febrile reactions – Bleomycin

Bleomycin causes fever within 48 hours in 50% of patients. Hydrocortisone prevents this reaction, and paracetamol can be used in its treatment.

Hydration - 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 kg, or symptoms of fluid overload

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

Anaphylactic-like reactions – Cisplatin, Etoposide
Anaphylactic-like reactions to Cisplatin and Etoposide have been reported. Facial oedema, bronchoconstriction, tachycardia and hypotension may occur within minutes of administration. Adrenaline, corticosteroids and antihistamines have been effectively employed to alleviate symptoms

DOSE MODIFICATIONS

As dose modification or delay of BEP regimen may compromise its efficacy, any modification of this regimen can only be done after discussion with a medical oncologist experienced in the treatment of Germ Cell tumours

Haematological Toxicity

Dose modifications should NOT be routinely continued through subsequent cycles in the absence of significant myelosuppression. Any dose modification must be discussed and approved by Specialist Consultant in treating Germ Cell tumours

Day 1
If at the start of any treatment cycle:

WBC < 1.5 x 10⁹/L
or Neutrophils < 0.5 x 10⁹/L
or Platelets < 50 x 10⁹/L

Delay therapy for 3 days
Repeat FBC and if recovered, resume therapy at full doses.
Discuss with Specialist Consultant

Day 8 and D15
FBC with Bleomycin is required for the clinical monitoring purposes - Treatment with Bleomycin will go ahead regardless of count

In the event of neutropenic fever or sepsis, no dose reduction will be made provided full haematological recovery has occurred by day 21.

In the case of repeated episodes of neutropenic sepsis or grade IV neutropenia, despite the use of G-CSF and prophylactic antibiotic, give Etoposide 100mg/m² per day for only 3 days and full doses of Cisplatin and Bleomycin in the next cycle, after discussion with Consultant

Renal Impairment:
GFR should be estimated 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 or EDTA

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Date: 19.05.10

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**Bleomycin** dose should be adjusted as follows:

<table>
<thead>
<tr>
<th>GFR (ml/min)</th>
<th>Bleomycin 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>

**Etoposide** dose should be adjusted as follows:

<table>
<thead>
<tr>
<th>GFR (ml/min)</th>
<th>Etoposide Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 60</td>
<td>Give 100%</td>
</tr>
<tr>
<td>40 – 60</td>
<td>Give 75%</td>
</tr>
<tr>
<td>&lt; 40</td>
<td>Give 50%</td>
</tr>
</tbody>
</table>

Cisplatin-induced nephrotoxicity is dose-related and cumulative. It manifests early by elevations in blood urea, creatinine and wasting of Potassium and Magnesium. Renal toxicity may be irreversible and is more prolonged and severe with repeated courses. **Cisplatin** dose should be adjusted as follows:

<table>
<thead>
<tr>
<th>GFR (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. Consider Carboplatin.</td>
</tr>
</tbody>
</table>

**Hepatic Impairment:**

- **Cisplatin:** No dose reduction necessary
- **Etoposide** and **Bleomycin** doses should be adjusted as follows:

<table>
<thead>
<tr>
<th>Bilirubin (µmol / L)</th>
<th>AST (units / L)</th>
<th>Etoposide Dose</th>
<th>Bleomycin Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>26 – 51 or 60 – 180</td>
<td>60 – 180</td>
<td>Give 50%</td>
<td>Clinical decision</td>
</tr>
<tr>
<td>&gt; 51 or &gt; 180</td>
<td>Clinical decision/ Omit</td>
<td>Clinical decision</td>
<td></td>
</tr>
</tbody>
</table>

**NON – HAEMATOLOGICAL TOXICITY**

For any Grade 3 – 4 toxicity, treatment should be deferred until recovery, and then continued with an appropriate dose reduction. Discuss with Consultant

Toxicities: Myelosuppression; nausea; vomiting; stomatitis; diarrhoea; nephrotoxicity; neurotoxicity; ototoxicity (low); pulmonary toxicity; electrolyte imbalances; skin and nail hyperpigmentation (20%); ulceration of finger tips; febrile reactions to Bleomycin; hypersensitivity reactions; Raynaud's syndrome; second malignancies; alopecia

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**Reason for Update:** Network Protocol Development

**Approved by:** Gynaecology Consultant: Ana Montes

**Version:** 3.1

**Supersedes:** All other versions

**Prepared by:** Maria Teresa Pacheca-Palomar April’10

**Approved by SELCN DTAC Chair: Janine Mansi**

**Date:** 19.05.10
Drug interactions:

**Bleomycin:**
- Cisplatin: decreased clearance of bleomycin
- Digoxin: decreased effect of Digoxin
- Phenytoin: decreased effect of Phenytoin

**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

**Cisplatin**
- Allopurinol, colchicine, probenecid, sulfinpyrazone: 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, 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

References:

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