Chemotherapy Protocol

**GERM CELL**

**BLEOMYCIN-CISPLATIN-ETOPOSIDE**

**(BEP 3 Day)**

**Regimen**
- Germ Cell – Bleomycin-Cisplatin-Etoposide (3 day BEP)

**Indication**
- In patients 40 years and below with;
  - metastatic non-seminomatous germ cell tumours
  - metastatic seminoma where radiotherapy is not appropriate

**Toxicity**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adverse Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleomycin</td>
<td>Pulmonary toxicity, rigors, skin pigmentation, nail changes</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>Neuropathy, nephrotoxicity, ototoxicity</td>
</tr>
<tr>
<td>Etoposide</td>
<td>Hypotension on rapid infusion, alopecia, hyperbilirubinemia</td>
</tr>
</tbody>
</table>

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

**Monitoring**

**Drugs**
- FBC, LFTs and U&Es prior to day 1, 8, 15 of the cycle
- AFP, HCG prior to day one of the cycle
- EDTA or calculated creatinine clearance
- Chest X-ray
- Consider pulmonary function tests before starting therapy. These should be repeated if respiratory symptoms develop during treatment, particularly a drop in oxygen saturation on exercise. The bleomycin should be stopped until the results of such investigations are known.

**Dose Modifications**

The dose modifications listed are for haematological, liver and renal function and drug specific toxicities only. Dose adjustments may be necessary for other toxicities as well.

In principle all dose reductions due to adverse drug reactions should not be re-escalated in subsequent cycles without consultant approval. It is also a general rule for chemotherapy that if a third dose reduction is necessary treatment should be stopped.
**Haematological**

Consider blood transfusion if patient symptomatic of anaemia or has a haemoglobin of less than 8g/dL.

Prior to each cycle the following criteria should be met:

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Eligible Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophil</td>
<td>equal to or more than 1x10^9/L</td>
</tr>
<tr>
<td>Platelets</td>
<td>equal to or more than 100 x10^9/L</td>
</tr>
</tbody>
</table>

This is a curative regimen. All dose reductions and delays should be discussed with the relevant consultant. In general if these levels are not met then treatment should be delayed for three days at a time. Treatment should re-start as soon as these haematological parameters are met. Dose delays rather than dose reductions are recommended.

Bleomycin should be administered on days 8 and 15 irrespective of the neutrophil and platelet count.

**Hepatic Impairment**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Bilirubin μmol/L</th>
<th>AST/ALT units/L</th>
<th>Dose (% of original dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleomycin</td>
<td></td>
<td></td>
<td>Clinical decision</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>N/A</td>
<td>N/A</td>
<td>No dose modification necessary</td>
</tr>
<tr>
<td>Etoposide</td>
<td>26-51 or 60-180</td>
<td></td>
<td>Consider dose reducing to 50%</td>
</tr>
<tr>
<td></td>
<td>greater than 51 or greater than 180</td>
<td>Clinical decision</td>
<td></td>
</tr>
</tbody>
</table>

**Renal Impairment**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Creatinine Clearance (ml/min)</th>
<th>Dose (% of original dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleomycin</td>
<td>50 or more</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>less than 50</td>
<td>Discuss with consultant and omit</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>60 or greater</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>If the creatinine clearance is below 60ml/min seek the advice of the consultant in charge of the patient. Consider changing to a 5 day schedule or using carboplatin rather than dose reducing cisplatin</td>
<td></td>
</tr>
<tr>
<td>Etoposide</td>
<td>greater than 50</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>15-50</td>
<td>75%</td>
</tr>
<tr>
<td></td>
<td>less than 15</td>
<td>50%</td>
</tr>
</tbody>
</table>
Other

Dose reductions or interruptions in therapy are not necessary for those toxicities that are considered unlikely to be serious or life threatening. For example, alopecia, altered taste or nail changes.

Bleomycin

The risk of bleomycin induced pneumonitis is greater in those individuals who are older than forty years of age, have a history of smoking, those with underlying lung disease, previous mediastinal radiotherapy or poor renal function. If pulmonary symptoms develop stop the bleomycin until they can be investigated fully and a diagnosis made.

Regimen

21 day cycle

Good prognosis - 3 cycles

Intermediate/poor prognosis - 4 cycles (if 4 cycles are required omit the day 8, 15 bleomycin on cycle 4 only)

3 cycles will be set in Aria

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Days</th>
<th>Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleomycin</td>
<td>30,000 IU</td>
<td>2, 8, 15</td>
<td>Intravenous infusion in 100ml sodium chloride 0.9% over 30 minutes</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>50mg/m²</td>
<td>1, 2</td>
<td>Intravenous infusion in 1000ml sodium chloride 0.9% with 20mmol potassium chloride over 120 minutes</td>
</tr>
<tr>
<td>Etoposide</td>
<td>165mg/m²</td>
<td>1, 2, 3</td>
<td>Intravenous infusion in 1000ml sodium chloride 0.9% over 60 minutes</td>
</tr>
</tbody>
</table>

Dose Information

- Aria is set to dose cap all regimens at 2.4m². This regimen must NOT be capped. Please override any doses that are capped.

- The maximum cumulative dose of bleomycin is 300 000 IU in people less than 40 years of age. Refer to SPC for further information in older patients.

- Cisplatin will be dose banded according to the CSCCN agreed bands

- Etoposide will be dose banded according to the CSCCN agreed bands
**Administration Information**

**Extravasation**

- Bleomycin – neutral
- Cisplatin – exfoliant
- Etoposide – irritant

**Additional Therapy**

- **Antiemetics**
  
  15-30 minutes prior to starting chemotherapy on day 1
  
  - aprepitant 125mg once a day on day 1 and 80mg once a day on days 2, 3
  - dexamethasone 4mg once a day on days 1, 2, 3 oral
  - metoclopramide 10mg three times a day when required oral
  - ondansetron 8mg twice a day on days 1, 2, 3, 4, 5 oral

- **On days of bleomycin administration**
  
  - hydrocortisone 100mg intravenous when required
  - chlorphenamine 10mg intravenous when required

- **Cisplatin pre-hydration as follows**
  
  - furosemide 40mg oral
  - sodium chloride 0.9% 1000ml with 16mmol magnesium sulphate and 20mmol potassium chloride over 60 minutes

- **Cisplatin post hydration as follows**
  
  - sodium chloride 0.9% 1000ml with 16mmol magnesium sulphate and 20mmol potassium chloride over 60 minutes

- **Ciprofloxacin** 500mg twice a day for 7 days starting on day 7 oral

- **Mouthwashes** according to local or national policy on the treatment of mucositis

- **Gastric protection** with a proton pump inhibitor or a H₂ antagonist may be considered in patients considered at high risk of GI ulceration or bleed.
- **Coding (OPCS)**
  - Procurement – X70.2
- **Delivery** – X72.1, X72.4

**References**
REGIMEN SUMMARY
Bleomycin-Cisplatin-Etoposide (3 day BEP)

Cycle 1, 2

Day 1

1. Aprepitant 125mg oral
2. Dexamethasone 4mg oral or intravenous
3. Ondansetron 8mg oral or intravenous
4. Furosemide 40mg oral or intravenous
5. Sodium chloride 0.9% 1000ml with magnesium sulphate 16mmol and potassium chloride 20mmol intravenous infusion over 60 minutes
6. Cisplatin 50mg/m² in 1000ml sodium chloride 0.9% with 20mmol potassium chloride intravenous infusion over 120 minutes
7. Sodium chloride 0.9% 1000ml with magnesium sulphate 16mmol and potassium chloride 20mmol intravenous infusion over 60 minutes
8. Etoposide 165mg/m² in 1000ml sodium chloride 0.9% intravenous infusion over 60 minutes

Take Home Medicines

9. Metoclopramide 10mg up to three times a day when required for the relief of nausea
10. Ondansetron 8mg to be taken on the evening of days 1, 2 and 3 of chemotherapy and then 8mg twice a day for two days after chemotherapy has finished
11. Ciprofloxacin 500mg twice a day for 7 days starting on day 7 of the cycle

Day 2

12. Aprepitant 80mg oral
13. Dexamethasone 4mg oral or intravenous
14. Ondansetron 8mg oral or intravenous
15. Furosemide 40mg oral or intravenous
16. Sodium chloride 0.9% 1000ml with magnesium sulphate 16mmol and potassium chloride 20mmol intravenous infusion over 60 minutes
17. Cisplatin 50mg/m² in 1000ml sodium chloride 0.9% with 20mmol potassium chloride intravenous infusion over 120 minutes
18. Sodium chloride 0.9% 1000ml with magnesium sulphate 16mmol and potassium chloride 20mmol intravenous infusion over 60 minutes

19. Etoposide 165mg/m² in 1000ml sodium chloride 0.9% intravenous infusion over 60 minutes

20. Bleomycin 30,000 IU in 100ml sodium chloride 0.9% intravenous infusion over 30 minutes

21. Chlorphenamine 10mg intravenous when required

22. Hydrocortisone 100mg intravenous when required

**Day 3**

23. Aprepitant 80mg oral

24. Dexamethasone 4mg oral or intravenous

25. Ondansetron 8mg oral or intravenous

26. Etoposide 165mg/m² in 1000ml sodium chloride 0.9% intravenous infusion over 60 minutes

**Day 8, 15**

27. Dexamethasone 8mg oral or intravenous

28. Bleomycin 30,000 IU in 100ml sodium chloride 0.9% intravenous infusion over 30 minutes

29. Chlorphenamine 10mg intravenous when required

30. Hydrocortisone 100mg intravenous when required

**Cycle 3**

**Day 1**

31. **Warning** – Check the number of cycles

Administration Instructions
If 4 cycles are required omit the day 8 and 15 bleomycin from cycle 4 when adding this cycle

32. Aprepitant 125mg oral

33. Dexamethasone 4mg oral or intravenous

34. Ondansetron 8mg oral or intravenous

35. Furosemide 40mg oral or intravenous

36. Sodium chloride 0.9% 1000ml with magnesium sulphate 16mmol and potassium chloride 20mmol intravenous infusion over 60 minutes
37. Cisplatin 50mg/m² in 1000ml sodium chloride 0.9% with 20mmol potassium chloride intravenous infusion over 120 minutes

38. Sodium chloride 0.9% 1000ml with magnesium sulphate 16mmol and potassium chloride 20mmol intravenous infusion over 60 minutes

39. Etoposide 165mg/m² in 1000ml sodium chloride 0.9% intravenous infusion over 60 minutes

Take Home Medicines

40. Metoclopramide 10mg up to three times a day when required for the relief of nausea

41. Ondansetron 8mg to be taken on the evening of days 1, 2 and 3 of chemotherapy and then 8mg twice a day for two days after chemotherapy has finished

42. Ciprofloxacin 500mg twice a day for 7 days starting on day 7 of the cycle

Day 2

43. Aprepitant 80mg oral

44. Dexamethasone 4mg oral or intravenous

45. Ondansetron 8mg oral or intravenous

46. Furosemide 40mg oral or intravenous

47. Sodium chloride 0.9% 1000ml with magnesium sulphate 16mmol and potassium chloride 20mmol intravenous infusion over 60 minutes

48. Cisplatin 50mg/m² in 1000ml sodium chloride 0.9% with 20mmol potassium chloride intravenous infusion over 120 minutes

49. Sodium chloride 0.9% 1000ml with magnesium sulphate 16mmol and potassium chloride 20mmol intravenous infusion over 60 minutes

50. Etoposide 165mg/m² in 1000ml sodium chloride 0.9% intravenous infusion over 60 minutes

51. Bleomycin 30,000 IU in 100ml sodium chloride 0.9% intravenous infusion over 30 minutes

52. Chlorphenamine 10mg intravenous when required

53. Hydrocortisone 100mg intravenous when required

Day 3

54. Aprepitant 80mg oral

55. Dexamethasone 4mg oral or intravenous

56. Ondansetron 8mg oral or intravenous
57. Etoposide 165mg/m² in 1000ml sodium chloride 0.9% intravenous infusion over 60 minutes

Day 8, 15

58. Dexamethasone 8mg oral or intravenous

59. Bleomycin 30,000 IU in 100ml sodium chloride 0.9% intravenous infusion over 30 minutes

60. Chlorphenamine 10mg intravenous when required

61. Hydrocortisone 100mg intravenous when required
### DOCUMENT CONTROL

<table>
<thead>
<tr>
<th>Version</th>
<th>Date</th>
<th>Amendment</th>
<th>Written By</th>
<th>Approved By</th>
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<tr>
<td>1.2</td>
<td>July 2015</td>
<td>Header changed Limits for renal and hepatic dose mods for etoposide updated Metoclopramide dose changed to 10mg Bolus removed from intravenous bolus throughout text Mucositis recommendation changed TTOs moved to day 1 in regimen summary OPCS code updated Disclaimer added</td>
<td>Donna Kimber Pharmacy Technician</td>
<td>Rebecca Wills Pharmacist</td>
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<tr>
<td>1.1</td>
<td>June 2013</td>
<td>Name changed to remove 40. Bleomycin dose reductions in renal impairment changed</td>
<td>Dr Deborah Wright Pharmacist</td>
<td>Dr Mathew Wheater Consultant Medical Oncologist</td>
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<tr>
<td>1</td>
<td>Dec 2012</td>
<td>None</td>
<td>Dr Deborah Wright Pharmacist</td>
<td>Dr Mathew Wheater Consultant Medical Oncologist</td>
</tr>
</tbody>
</table>

This chemotherapy protocol has been developed as part of the chemotherapy electronic prescribing project. This was and remains a collaborative project that originated from the former CSCCN. These documents have been approved on behalf of the following Trusts;

- Hampshire Hospitals NHS Foundation Trust
- NHS Isle of Wight
- Portsmouth Hospitals NHS Trust
- Salisbury Hospitals NHS Foundation Trust
- University Hospital Southampton NHS Foundation Trust
- Western Sussex Hospitals NHS Foundation Trust

All actions have been taken to ensure these protocols are correct. However, no responsibility can be taken for errors which occur as a result of following these guidelines.