Chemotherapy Protocol

GERM CELL

BLEOMYCIN-CISPLATIN-ETOPOSIDE

(BEP 5 Day)

Regimen

- Germ Cell – Bleomycin-Cisplatin-Etoposide (5 day BEP)

Indication

- In patients 40 years and below with;
  - metastatic non-seminomatous germ cell tumours
  - metastatic seminoma where radiotherapy is not appropriate
  - renal impairment or a poor performance status

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, hyperbilirubineamia</td>
</tr>
</tbody>
</table>

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

Monitoring

- FBC, LFTs and U&Es on day one of the cycle
- AFP, HCG prior to day one of the cycle
- 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. 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.
Patients are being treated with curative intent therefore dose modifications and delays should be kept to a minimum. Please discuss all dose reductions / delays with the relevant consultant before prescribing. The approach may be different depending on the clinical circumstances.

**Haematological**

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

Prior to each cycle the following criteria must 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 0.5x10^9/L</td>
</tr>
<tr>
<td>Platelets</td>
<td>equal to or more than 100x10^9/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.

**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</td>
<td>greater than 180</td>
<td>Clinical decision</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 59ml/min or below please refer to the responsible consultant for advice</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.

For all other non-haematological NCI-CTC grade 3 and above toxicities delay treatment until the adverse effect has resolved to NCI-CTC grade 1 or below. The dose of the causative agent(s) may then be reduced or discontinued at the discretion of the consultant.

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

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
21 day cycle for 3 cycles

<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>20mg/m²</td>
<td>1,2,3,4,5</td>
<td>Intravenous infusion in 1000ml sodium chloride 0.9% with 20mmol potassium chloride over 60 minutes</td>
</tr>
<tr>
<td>Etoposide</td>
<td>100mg/m²</td>
<td>1,2,3,4,5</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.
- Cisplatin will be dose banded according to the agreed bands
- Etoposide will be dose banded according to the agreed bands

Administration Information

Extravasation

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

Additional Therapy

- Antiemetics
  - 15 – 30 minutes prior to chemotherapy
    - aprepitant 125mg once a day on day 1
    - aprepitant 80mg once a day on days 2, 3
    - dexamethasone 4mg once a day on days 1, 2, 3, 4, 5, 6, 7 oral
    - metoclopramide 10mg three times a day when required oral
    - ondansetron 8mg twice a day on days 1, 2, 3, 4, 5, 6, 7 oral
  - On days of bleomycin administration
    - hydrocortisone 100mg intravenous when required
    - chlorphenamine 10mg intravenous when required
  - Cisplatin pre-hydration as follows
    - furosemide 40mg oral or intravenous as required
    - sodium chloride 0.9% 1000ml with 8mmol magnesium sulphate over 60 minutes
• Cisplatin post hydration
  - sodium chloride 0.9% 1000ml over 240 minutes

• Ciprofloxacin 500mg twice a day for 7 days starting on day 8 of the cycle

• Consider growth factor support according to local policy, for example;
  - filgrastim or bioequivalent 30 million units once a day for seven days starting on day seven of the cycle subcutaneous
  - lenograstim or bioequivalent 33.6 million units once a day for seven days starting on day seven of the cycle subcutaneous
  - pegfilgrastim or bioequivalent 6mg once a day on day seven of the cycle

• 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 – X70.3

• Delivery – N/A

References
REGIMEN SUMMARY

Bleomycin-Cisplatin-Etoposide (5 day BEP)

Cycle 1, 2, 3, 4

Day 1

1. Aprepitant 125mg oral
2. Dexamethasone 4mg oral or intravenous
3. Metoclopramide 10mg oral or intravenous
4. Ondansetron 8mg oral or intravenous bolus
5. Furosemide 40mg oral or intravenous when required for the maintenance of diuresis
6. Sodium chloride 0.9% 1000ml with magnesium sulphate 8mmol intravenous infusion over 60 minutes
7. Cisplatin 20mg/m² in 1000ml sodium chloride 0.9% with 20mmol potassium chloride intravenous infusion over 60 minutes
8. Sodium chloride 0.9% 1000ml over 240 minutes
9. Etoposide 100mg/m² in 1000ml sodium chloride 0.9% intravenous infusion over 60 minutes

Take Home Medicines

10. Dexamethasone 4mg once a day in the morning for 2 days starting on day 6 of the cycle oral
11. Metoclopramide 10mg up to three times a day when required for the relief of nausea oral
12. Ondansetron 8mg to be taken on the evening of days 1, 2, 3, 4 and 5 of chemotherapy and 8mg twice a day for 2 days starting on day 6 of the cycle oral
13. Ciprofloxacin 500mg twice a day for 7 days starting on day 8 of the cycle oral

Day 2

14. Aprepitant 80mg oral
15. Dexamethasone 4mg oral or intravenous
16. Metoclopramide 10mg oral or intravenous
17. Ondansetron 8mg oral or intravenous bolus
18. Furosemide 40mg oral or intravenous when required for the maintenance of diuresis
19. Sodium chloride 0.9% 1000ml with magnesium sulphate 8mmol intravenous infusion over 60 minutes

20. Cisplatin 20mg/m² in 1000ml sodium chloride 0.9% with 20mmol potassium chloride intravenous infusion over 60 minutes

21. Sodium chloride 0.9% 1000ml over 30 minutes

22. Etoposide 100mg/m² in 1000ml sodium chloride 0.9% intravenous infusion over 60 minutes

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

24. Chlorphenamine 10mg intravenous when required for bleomycin reactions

25. Hydrocortisone 100mg intravenous when required for bleomycin reactions

**Days 3**

26. Aprepitant 80mg oral

27. Dexamethasone 4mg oral or intravenous

28. Metoclopramide 10mg oral or intravenous

29. Ondansetron 8mg oral or intravenous bolus

30. Furosemide 40mg oral or intravenous when required for the maintenance of diuresis

31. Sodium chloride 0.9% 1000ml with magnesium sulphate 8mmol intravenous infusion over 60 minutes

32. Cisplatin 20mg/m² in 1000ml sodium chloride 0.9% with 20mmol potassium chloride intravenous infusion over 60 minutes

33. Sodium chloride 0.9% 1000ml over 240 minutes

34. Etoposide 100mg/m² in 1000ml sodium chloride 0.9% intravenous infusion over 60 minutes

**Days 4, 5**

35. Dexamethasone 4mg oral or intravenous

36. Metoclopramide 10mg oral or intravenous

37. Ondansetron 8mg oral or intravenous bolus

38. Furosemide 40mg oral or intravenous when required for the maintenance of diuresis

39. Sodium chloride 0.9% 1000ml with magnesium sulphate 8mmol intravenous infusion over 60 minutes
40. Cisplatin 20mg/m² in 1000ml sodium chloride 0.9% with 20mmol potassium chloride intravenous infusion over 60 minutes

41. Sodium chloride 0.9% 1000ml over 240 minutes

42. Etoposide 100mg/m² in 1000ml sodium chloride 0.9% intravenous infusion over 60 minutes

Day 8, 15

43. Dexamethasone 8mg oral or intravenous

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

45. Chlorphenamine 10mg intravenous when required

46. Hydrocortisone 100mg intravenous when required
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 Hospital 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.