

## Chemotherapy Protocol

### GERM CELL

#### BLEOMYCIN-CISPLATIN-ETOPOSIDE

##### (BEP 5 Day Modified)

#### Regimen

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

#### Indication

- In patients 41 years and above with;
  - metastatic non-seminomatous germ cell tumours
  - metastatic seminoma where radiotherapy is not appropriate
  - renal impairment or a poor performance status

#### Toxicity

Drug	Adverse Effect
Bleomycin	Pulmonary toxicity, rigors, skin pigmentation, nail changes
Cisplatin	Neuropathy, nephrotoxicity, ototoxicity
Etoposide	Hypotension on rapid infusion, alopecia, hyperbilirubinaemia

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 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

Criteria	Eligible Level
Neutrophil	equal to or more than $0.5 \times 10^9/L$
Platelets	equal to or more than $100 \times 10^9/L$

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

Drug	Bilirubin $\mu\text{mol/L}$		AST/ALT units/L	Dose (% of original dose)
Bleomycin				Clinical decision
Cisplatin	N/A		N/A	No dose modification necessary
Etoposide	26-51	or	60-180	Consider dose reducing to 50%
	greater than 51	or	greater than 180	Clinical decision

## Renal Impairment

Drug	Creatinine Clearance (ml/min)	Dose (% of original dose)
Bleomycin	50 or more	100%
	less than 50	discuss with consultant and omit
Cisplatin	60 or greater	100%
	If the creatinine clearance is 59ml/min or below please refer to the responsible consultant for advice	
Etoposide	greater than 50	100%
	15-50	75%
	less than 15	50%

## 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

### 21 day cycle for 4 cycles

Drug	Dose	Days	Administration
Bleomycin	30,000 IU	2	Intravenous infusion in 100ml sodium chloride 0.9% over 30 minutes
Cisplatin	20mg/m <sup>2</sup>	1,2,3,4,5	Intravenous infusion in 1000ml sodium chloride 0.9% with 20mmol potassium chloride over 60 minutes
Etoposide	100mg/m <sup>2</sup>	1,2,3,4,5	Intravenous infusion in 1000ml sodium chloride 0.9% over 60 minutes

### Dose Information

- Aria is set to dose cap all regimens at 2.4m<sup>2</sup>. This regimen must NOT be capped. Please override any doses that are capped.
- Patients over the age of 40 are at increased risk of pulmonary toxicity and therefore the maximum cumulative dose of bleomycin is limited to 120 000IU in this protocol.
- 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 for one 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 H<sub>2</sub> antagonist may be considered in patients considered at high risk of GI ulceration or bleed.

#### Coding (OPCS)

- Procurement – X70.3
- Delivery – N/A

#### References

- 1.de Wit R, Roberts JT, Wilkinson PM et al. Equivalence of 3 cycle BEP versus 4 cycles and of the 5 day schedule versus 3 days per cycle in good-prognosis germ cell cancer: a randomised study of the European Organisation for Research and Treatment of Cancer Genitourinary Tract Cancer Cooperative Group and the Medical Research Council. J Clin Oncol 2001; 19: 1629-1640.
- 2.de Wit R, Stoter G, et al. Four cycles of BEP versus four cycles of VIP in patients with intermediate-prognosis metastatic testicular non seminoma: A randomised study of the EORTC Genitourinary Tract Cancer Cooperative Group. Br J Cancer 1998; 78(6): 828-832.
- 3.Nichols C, Catalano P, Crawford E et al. Randomised comparison of cisplatin and etoposide and either bleomycin or ifosfamide in the treatment of advanced disseminated germ cell tumours: An Eastern Cooperative Oncology Group, Southwest Oncology Group and Cancer and Leukemia Group B study. J Clin Oncol 1998; 16: 1287-1293.
- 5.Fossa SD, Kaye SB, Mead GM, Cullen MH, De Wit R, Borogi J, Van Groeningen C, De Mulder P, Stenning S and De Prijck L. Filgrastim (G-CSF) during combination chemotherapy of patients with poor prognosis metastatic germ cell malignancy (A phase III trial of the EORTC GU group/MRC testicular tumour working party) J Clin Oncol 1998; 16: 716-724

## REGIMEN SUMMARY

Bleomycin-Cisplatin-Etoposide (5 day-Mod-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 to maintain diuresis
6. Sodium chloride 0.9% 1000ml with magnesium sulphate 8mmol intravenous infusion over 30 minutes
7. Cisplatin 20mg/m<sup>2</sup> 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/m<sup>2</sup> 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 30 minutes
20. Cisplatin 20mg/m<sup>2</sup> in 1000ml sodium chloride 0.9% with 20mmol potassium chloride intravenous infusion over 60 minutes
21. Sodium chloride 0.9% 1000ml over 240 minutes
22. Etoposide 100mg/m<sup>2</sup> 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**

1. Aprepitant 80mg 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/m<sup>2</sup> 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/m<sup>2</sup> in 1000ml sodium chloride 0.9% intravenous infusion over 60 minutes

### **Days 4, 5**

1. Dexamethasone 4mg oral or intravenous
2. Metoclopramide 10mg oral or intravenous
3. Ondansetron 8mg oral or intravenous bolus
4. Furosemide 40mg oral or intravenous when required for the maintenance of diuresis
5. Sodium chloride 0.9% 1000ml with magnesium sulphate 8mmol intravenous infusion over 60 minutes

6. Cisplatin  $20\text{mg}/\text{m}^2$  in 1000ml sodium chloride 0.9% with 20mmol potassium chloride intravenous infusion over 60 minutes
7. Sodium chloride 0.9% 1000ml over 240 minutes
8. Etoposide  $100\text{mg}/\text{m}^2$  in 1000ml sodium chloride 0.9% intravenous infusion over 60 minutes



## DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1	July 2017	None	Dr Deborah Wright Pharmacist	Dr Emma Killick Consultant Medical Oncologist

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.