

Chemotherapy Protocol

GERM CELL

BLEOMYCIN-CISPLATIN-ETOPOSIDE

(BEP 5 Day Modified)

In-Patient Regimen

Regimen

- Germ Cell – InP-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 blood transfusion if patient 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 ²	1,2,3,4,5	Intravenous infusion in 1000ml sodium chloride 0.9% with 20mmol potassium chloride over 60 minutes
Etoposide	100mg/m ²	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 2.4m². 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 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

This is an inpatient regimen please ensure all supportive and take home medication not on Aria are prescribed on the inpatient chart or general electronic prescribing system.

- 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% 500ml with 8mmol magnesium sulphate over 30 minutes
- Cisplatin post hydration
 - sodium chloride 0.9% 500ml over 30 minutes

- Ciprofloxacin 500mg twice a day for 7 days starting on day 8 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

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

InP-Bleomycin-Cisplatin-Etoposide (5 day-Mod-BEP)

Other than those listed below, supportive medication for this regimen will not appear in Aria as prescribed agents. The administration instructions for each warning describes the agents which must be prescribed on the in-patient chart or general electronic prescribing system

Cycle 1, 2, 3, 4

Day 1

1. Warning – Check supportive medicines prescribed

Administration Instructions

- 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
- furosemide 40mg when required oral
- chlorphenamine 10mg intravenous for bleomycin reactions
- hydrocortisone 100mg intravenous for bleomycin reactions
- ciprofloxacin 500mg twice a day for 7 days starting on day 8 oral

2. Sodium chloride 0.9% 500ml with magnesium sulphate 8mmol intravenous infusion over 30 minutes
3. Cisplatin 20mg/m² in 1000ml sodium chloride 0.9% with 20mmol potassium chloride intravenous infusion over 60 minutes
4. Sodium chloride 0.9% 500ml over 30 minutes
5. Etoposide 100mg/m² in 1000ml sodium chloride 0.9% intravenous infusion over 60 minutes

Day 2

6. Warning – Check supportive medicines prescribed

Administration Instructions

- 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
- furosemide 40mg when required oral
- chlorphenamine 10mg intravenous for bleomycin reactions
- hydrocortisone 100mg intravenous for bleomycin reactions
- ciprofloxacin 500mg twice a day for 7 days starting on day 8 oral

7. Sodium chloride 0.9% 500ml with magnesium sulphate 8mmol intravenous infusion over 30 minutes
8. Cisplatin 20mg/m² in 1000ml sodium chloride 0.9% with 20mmol potassium chloride intravenous infusion over 60 minutes
9. Sodium chloride 0.9% 500ml over 30 minutes
10. Etoposide 100mg/m² in 1000ml sodium chloride 0.9% intravenous infusion over 60 minutes

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

Days 3, 4, 5

12. Warning – Check supportive medicines prescribed

Administration Instructions

- 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
- furosemide 40mg when required oral
- chlorphenamine 10mg intravenous for bleomycin reactions
- hydrocortisone 100mg intravenous for bleomycin reactions
- ciprofloxacin 500mg twice a day for 7 days starting on day 8 oral

13. Sodium chloride 0.9% 500ml with magnesium sulphate 8mmol intravenous infusion over 30 minutes

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

15. Sodium chloride 0.9% 500ml over 30 minutes

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

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1.2	July 2015	Header changed Renal and hepatic dose mods updated for etoposide Metoclopramide dose changed to 10mg Bolus removed from intravenous bolus throughout text Mucositis recommendation changed OPCS code updated Disclaimer added	Donna Kimber Pharmacy Technician	Rebecca Wills Pharmacist
1.1	June 2013	Name changed throughout. Bleomycin dose reductions in renal impairment changed	Dr Deborah Wright Pharmacist	Dr Mathew Wheeler Consultant Medical Oncologist
1	Jan 2013	None	Rebecca Wills Pharmacist Dr Deborah Wright Pharmacist	Dr Joanna Gale Consultant Medical Oncologist Dr Mathew Wheeler 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 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.