Chemotherapy Protocol

GERM CELL

BLEOMYCIN-CISPLATIN-ETOPOSIDE

(BEP 3 Day Modified)

Regimen

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

Indication

- In patients 41 years and above with;
    - metastatic non-seminomatous germ cell tumours
    - metastatic seminoma where radiotherapy is not appropriate

Toxicity

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

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 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;

Criteria	Eligible Level
Neutrophil	equal to or more than $1x10^9$/L
Platelets	equal to or more than $100x10^9$/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 µmol/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	omit and discuss with consultant
Cisplatin	60 or greater	100%
	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	
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.

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	50mg/m^2	1, 2	Intravenous infusion in 1000ml sodium chloride 0.9% with 20mmol potassium chloride over 120 minutes
Etoposide	165mg/m^2	1, 2, 3	Intravenous infusion in 1000ml sodium chloride 0.9% over 60 minutes

Dose Information

- Aria is set to dose cap all regimens at 2.4m^2. 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 H_2 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

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.
4.Cullen M, Steven N, Billingham L et al (2005). Antibacterial prophylaxis after chemotherapy for solid tumors and lymphomas. NEJM 353 (10): 988-998
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 (3 day-Mod-BEP)

Cycle 1, 2, 3, 4

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/m^2 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/m^2 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/m^2 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/m^2 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/m^2 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 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	Donna Kimber Pharmacy Technician	Rebecca Wills Pharmacist
1.1	June 2013	Name of regimen changed throughout to “modified”. Bleomycin dose reductions in renal impairment changed	Dr Deborah Wright Pharmacist	Dr Mathew Wheater Consultant Medical Oncologist
1	Dec 2012	None	Rebecca Wills Pharmacist Dr Deborah Wright Pharmacist	Dr Joanna Gale Consultant Medical Oncologist Dr Mathew Wheater 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.