

Chemotherapy Protocol

LYMPHOMA

BLEOMYCIN-CYCLOPHOSPHAMIDE-DOXORUBICIN-ETOPOSIDE-PREDNISOLONE- PROCARBAZINE-VINCRIStINE

(BEACOPP Escalated)

Regimen

- Lymphoma – BEACOPP Escalated -Bleomycin-Cyclophosphamide-Doxorubicin-Etoposide-Prednisolone-Procarbazine-Vincristine

Indication

- Hodgkin's Lymphoma

Toxicity

Drug	Adverse Effect
Bleomycin	Pulmonary toxicity, rigors, skin pigmentation, nail changes
Cyclophosphamide	Dysuria, haemorrhagic cystitis (rare), taste disturbances
Doxorubicin	Cardiotoxicity, urinary discolouration (red)
Etoposide	Hypotension on rapid infusion, alopecia, hyperbilirubinaemia
Prednisolone	Weight gain, GI disturbances, hyperglycaemia, CNS disturbances, cushingoid changes, glucose intolerance
Procarbazine	Insomnia, ataxia, hallucinations, headache
Vincristine	Peripheral neuropathy, constipation, jaw pain

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

Patients diagnosed with Hodgkin's Lymphoma carry a lifelong risk of transfusion associated graft versus host disease (TA-GVHD). Where blood products are required these patients must receive only irradiated blood products for life. Local blood transfusion departments must be notified as soon as a diagnosis is made and the patient must be issued with an alert card to carry with them at all times.

Monitoring

Drugs

- FBC, LFTs and U&Es prior to day one of treatment
- Ensure adequate cardiac function before starting therapy. Baseline LVEF should be measured in patients with a history of cardiac problems, cardiac risk factors or in the elderly. Discontinue doxorubicin if cardiac failure develops.
- 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 some limited 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.

Please discuss all dose reductions / delays with the relevant consultant before prescribing, if appropriate. The approach may be different depending on the clinical circumstances.

Haematological

Dose modifications for haematological toxicity below are for general guidance only. Always refer to the responsible consultant as any dose reductions or delays will be dependent on clinical circumstances and treatment intent. Low counts can be a consequence of bone marrow infiltration as well as drug toxicity.

Cycles should be repeated on day 22 provided the white cell count is greater than $2.5 \times 10^9/L$ and the platelet count is greater than $80 \times 10^9/L$

Day 8 drugs should be given on schedule and at full dose regardless of blood counts.

Dose modifications based on haematological parameters apply to cyclophosphamide and etoposide only

Doses should be reduced in subsequent cycles if, in any given cycle:

WBC is less than $1.0 \times 10^9 /L$ for more than four days

Platelets are less than $25 \times 10^9 /L$ at any time

There is infection, mucositis or other adverse effect that requires a two-week delay in treatment.

After each such event, the doses of cyclophosphamide and etoposide should be reduced by one level on a five-level scale from escalated to standard doses as shown below. If toxic effects occur in two successive cycles, standard doses should be used for all subsequent cycles.

Drug	Level 1 escalated dose	Level 2	Level 3	Level 4	Level 5 standard dose
Cyclophosphamide	1250mg/m ²	1100mg/m ²	950mg/m ²	800mg/m ²	650mg/m ²
Etoposide	200mg/m ²	175mg/m ²	150mg/m ²	125mg/m ²	100mg/m ²

Growth factors are mandatory as part of this regimen.

Consider blood transfusion if patient symptomatic of anaemia or has a haemoglobin of less than 8g/dL. **Irradiated blood products must be used in Hodgkin's Lymphoma patients.**

Hepatic Impairment

If abnormal liver function tests are lymphoma related proceed with treatment at full dose unless there is an overriding clinical reason not to do so.

Drug	Bilirubin μmol/L		AST/ALT units/L	Dose (% of original dose)
Bleomycin				Clinical decision. Increased risk of lung dysfunction
Cyclophosphamide	N/A		N/A	Evidence suggests dose modification not necessary
Doxorubicin	less than *30	and	2-3xULN	75%
	*30-50	and/or	more than 3xULN	50%
	51-85		N/A	25%
	more than 85		N/A	Omit
Etoposide	*30-51	or	60-180	50%
	more than 51	or	more than 180	clinical decision
Procarbazine	more than 50			Consider dose reduction
	more than 85	or	more than 180	Omit
Vincristine	*30-51	or	60-180	50%
	more than 51	and	normal	50%
	more than 51	and	more than 180	Omit

* Limits reflect local practice and may vary from published sources

Renal Impairment

Drug	Creatinine Clearance (ml/min)	Dose (% of original dose)
Bleomycin	more than 50	100%
	10-50	75%
	less than 10	50%
Cyclophosphamide	more than 20	100%
	10-20	75%
	less than 10	50%
Doxorubicin	less than 10	Consider dose reduction in severe renal failure
Etoposide	more than 50	100%
	15-50	75%
	less than 15	50%
Procarbazine	serum creatinine more than 177 μ mol/L	50%
	less than 10	Not recommended
Vincristine	N/A	no dose adjustment needed

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, poor renal function or who require growth factors. If pulmonary symptoms develop stop the bleomycin until they can be investigated fully and a diagnosis made.

Doxorubicin

Discontinue doxorubicin if cardiac failure develops.

Etoposide

Where significant reductions in albumin levels occur consider reducing the dose of etoposide.

[Vincristine](#)

Reduce the vincristine dose to 1mg if an NCI-CTC grade 2 motor or grade 3 sensory neurological toxicity occurs. For higher toxicity grades or if toxicity increases despite dose reduction stop the vincristine.

[Regimen](#)

21 day cycle for up to 8 cycles

6 cycles will be set in Aria

Drug	Dose	Days	Administration
Bleomycin	10,000 international units/m ²	8	Intravenous bolus over 10 minutes
Cyclophosphamide	1250mg/m ²	1	Intravenous infusion in 500ml sodium chloride 0.9% over 60 minutes
Doxorubicin	35mg/m ²	1	Intravenous bolus over 10 minutes
Etoposide	200mg/m ²	1, 2, 3	Intravenous infusion in 1000ml sodium chloride 0.9% over 60 minutes
Prednisolone	40mg/m ²	1-14	Oral
Procarbazine	100mg/m ²	1-7	Oral
Vincristine	1.4mg/m ² (max 2mg)	8	Intravenous bolus in 50ml sodium chloride 0.9% over 10 minutes
G-CSF	1 dose	9-13	Subcutaneous

[Dose Information](#)

- Bleomycin will be dose rounded to the nearest 1000 International Units (up if halfway)
- The maximum cumulative dose of bleomycin is 500,000 international units in people less than sixty years of age. Refer to SPC for further information in older patients.
- Cyclophosphamide will be dose banded in accordance with the national dose bands (multi syringe 20mg/ml)
- Doxorubicin will be dose banded in accordance with the national dose bands (multi syringe 2mg/ml)
- The maximum lifetime cumulative dose of doxorubicin is 450mg/m². However prior radiotherapy to mediastinal / pericardial area should receive a lifetime cumulative doxorubicin dose of no more than 400mg/m².
- Etoposide (intravenous) will be dose banded in accordance with the national dose bands (20mg/ml)

- Prednisolone is available as 5mg and 25mg tablets the dose will be rounded to the nearest 5mg (up if halfway)
- Procarbazine is available as 50mg capsules. To facilitate alternate day dosing in ARIA the dose will be rounded to the nearest 25mg (up if halfway).
 - If the calculated daily dose is 125mg please dispense 150mg alternating with 100mg once a day
 - If the calculated daily dose is 175mg please dispense 200mg alternating with 150mg once a day
 - If the calculated daily dose is 225mg please dispense 250mg alternating with 200mg once a day
- Vincristine will be dose banded in accordance with the national dose bands (1mg/ml)
- The maximum dose of vincristine is 2mg.

[Administration Information](#)

Extravasation

- Bleomycin - neutral
- Cyclophosphamide – neutral
- Doxorubicin – vesicant
- Etoposide – irritant
- Vincristine - vesicant

Other

- Prednisolone should be taken in the morning with or after food.
- Procarbazine has weak MAOI activity. Alcohol and foods rich in tyramine (including some wines and cheeses) should be avoided. Do not use with other MAOIs.

[Additional Therapy](#)

- Antiemetics

15-30 minutes prior to chemotherapy (days 1-3)

- ondansetron 8mg oral or intravenous

At least 15 minutes prior to chemotherapy (days 1-3)

- prednisolone 40mg/m² oral to be administered in clinic on day 1 and self-administered by the patient on the morning of treatment on days 2 and 3 (this is part of the chemotherapy schedule as well as an anti-emetic)

As take home medication

- metoclopramide 10mg three times a day when required oral
- ondansetron 8mg to be taken in the evening on days 1-3 then twice a day for the 2 days after chemotherapy has finished
- Allopurinol 300mg once a day for 7 days oral for the first cycle only
- Growth factor on days 9 to 13. For example:
 - filgrastim or bioequivalent 30 million units once a day for 5 days from day 9 subcutaneous
 - lenograstim or bioequivalent 33.6 million units once a day for 5 days from day 9 subcutaneous
- Aciclovir 400mg twice a day oral
- Co-trimoxazole 960mg once a day oral on Monday, Wednesday and Friday only
- Fluconazole 100mg once day 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.

[Additional Information](#)

- The National Patient Safety Agency report NPSA/2008/RRR04 must be followed in relation to intravenous administration of vinca alkaloids.

[Coding \(OPCS\)](#)

- Procurement – X70.3
- Delivery – X72.1, X72.4

References

1. Johnson P, Federico M, Kirkwood A, Fossà, A et al. Adapted Treatment Guided by Interim PET-CT Scan in Advanced Hodgkin's Lymphoma N Engl J Med 2016; 374:2419-2429
2. Gallamini A, Tarella C, Viviani S, Rossi A et al. Early Chemotherapy Intensification with Escalated BEACOPP in Patients with Advanced-Stage Hodgkin Lymphoma with a Positive Interim Positron Emission Tomography/Computed Tomography Scan After Two ABVD Cycles: Long-Term Results of the GITIL/FIL HD 0607 Trial. J Clin Oncol. 2018 Feb 10;36(5):454-462
3. Escalated-dose BEACOPP in the treatment of patients with advanced-stage Hodgkin's lymphoma: 10 years of follow-up of the GHSG HD9 study. J Clin Oncol. 2009 Sep 20;27(27):4548-54. Engert A, Diehl V, Franklin J et al.

REGIMEN SUMMARY

BEACOPP Escalated-Bleomycin-Cyclophosphamide-Doxorubicin-Etoposide-Prednisolone-Procarbazine-Vincristine

Cycle 1 Day 1

1. **Warning –Check blood transfusion status**
Administration Instructions
Patients with HODGKIN'S lymphoma carry a lifelong risk of transfusion associated graft versus host disease. Where blood products are required these patients must receive ONLY IRRADIATED BLOOD PRODUCTS for life. Ensure transfusion departments are notified and the patient has been issued with an alert card to carry with them at all times.
2. **Prednisolone 40mg/m² oral**
Administration Instructions
Administer 15-30 minutes prior to chemotherapy.
3. **Ondansetron 8mg oral or intravenous**
Administration Instructions
Administer 15-30 minutes prior to chemotherapy
4. **Doxorubicin 35mg/m² intravenous bolus over 10 minutes**
5. **Etoposide 200mg/m² intravenous infusion in 1000ml sodium chloride 0.9% over 60 minutes**
6. **Cyclophosphamide 1250mg/m² intravenous infusion in 500ml sodium chloride 0.9% over 60 minutes**

Take Home Medicines (Day 1 only)

7. **Prednisolone 40mg/m² once a day oral for 13 days**
Administration Instructions
Starting on day 2 of the cycle
8. **Procarbazine 100mg/m² once a day oral for 7 days**
Administration Instructions
Procarbazine is available as 50mg capsules. To facilitate alternate day dosing in ARIA the dose will be rounded to the nearest 25mg (up if halfway).
If the calculated daily dose is 125mg please dispense 150mg alternating with 100mg once a day
If the calculated daily dose is 175mg please dispense 200mg alternating with 150mg once a day
If the calculated daily dose is 225mg please dispense 250mg alternating with 200mg once a day
9. **Growth Factor as directed**
Administration Instructions
Growth factor as per local formulary choice:
 - filgrastim or bioequivalent 30 million units once a day for 5 days starting on day 9 of the cycle subcutaneous
 - lenograstim or bioequivalent 33.6 million units once a day for 5 days starting on day 9 of the cycle subcutaneous
10. **Metoclopramide 10mg three times a day when required oral**
11. **Ondansetron 8mg taken on the evening of days 1, 2 and 3 then 8mg twice a day for the 2 days after chemotherapy**
12. **Allopurinol 300mg once a day oral for 7 days**
13. **Aciclovir 400mg twice a day oral for 21 days**

14. Co-trimoxazole 960mg once a day on Monday, Wednesday and Friday oral for 21 days

15. Fluconazole 100mg once a day oral for 21 days

Cycle 1 Day 2

16. Ondansetron 8mg oral or intravenous

Administration Instructions

Administer 15-30 minutes prior to chemotherapy

17. Etoposide 200mg/m² intravenous infusion in 1000ml sodium chloride 0.9% over 60 minutes

Cycle 1 Day 3

18. Ondansetron 8mg oral or intravenous

Administration Instructions

Administer 15-30 minutes prior to chemotherapy

19. Etoposide 200mg/m² intravenous infusion in 1000ml sodium chloride 0.9% over 60 minutes

Cycle 1 Day 8

20. Vincristine 1.4mg/m² (max 2mg) intravenous bolus in 50ml sodium chloride 0.9% over 10 minutes

21. Bleomycin 10,000 international units/m² intravenous bolus over 10 minutes

22. Hydrocortisone 100mg intravenous when required for the treatment of bleomycin related reactions

Cycles 2, 3, 4, 5 & 6 Day 1

1. Prednisolone 40mg/m² oral

Administration Instructions

Administer 15-30 minutes prior to chemotherapy.

2. Ondansetron 8mg oral or intravenous

Administration Instructions

Administer 15-30 minutes prior to chemotherapy

3. Doxorubicin 35mg/m² intravenous bolus over 10 minutes

4. Etoposide 200mg/m² intravenous infusion in 1000ml sodium chloride 0.9% over 60 minutes

5. Cyclophosphamide 1250mg/m² intravenous infusion in 500ml sodium chloride 0.9% over 60 minutes

Take Home Medicines (Day 1 only)

6. Prednisolone 40mg/m² once a day oral for 13 days

Administration Instructions

Starting on day 2 of the cycle

7. Procarbazine 100mg/m² once a day oral for 7 days

Administration Instructions

Procarbazine is available as 50mg capsules. To facilitate alternate day dosing in ARIA the dose will be rounded to the nearest 25mg (up if halfway).

If the calculated daily dose is 125mg please dispense 150mg alternating with 100mg once a day

If the calculated daily dose is 175mg please dispense 200mg alternating with 150mg once a day

If the calculated daily dose is 225mg please dispense 250mg alternating with 200mg once a day

8. Growth Factor as directed

Administration Instructions

Growth factor as per local formulary choice:

- filgrastim or bioequivalent 30 million units once a day for 5 days starting on day 9 of the cycle subcutaneous
- lenograstim or bioequivalent 33.6 million units once a day for 5 days starting on day 9 of the cycle subcutaneous

9. Metoclopramide 10mg three times a day when required oral

10. Ondansetron 8mg taken on the evening of days 1, 2 and 3 then 8mg twice a day for the 2 days after chemotherapy

11. Aciclovir 400mg twice day oral for 21 days

12. Co-trimoxazole 960mg once a day on Monday, Wednesday and Friday oral for 21 days

13. Fluconazole 100mg once a day for 21 days

Cycles 2, 3, 4, 5 & 6 Day 2

14. Ondansetron 8mg oral or intravenous

Administration Instructions

Administer 15-30 minutes prior to chemotherapy

15. Etoposide 200mg/m² intravenous infusion in 1000ml sodium chloride 0.9% over 60 minutes

Cycles 2, 3, 4, 5 & 6 Day 3

16. Ondansetron 8mg oral or intravenous

Administration Instructions

Administer 15-30 minutes prior to chemotherapy

17. Etoposide 200mg/m² intravenous infusion in 1000ml sodium chloride 0.9% over 60 minutes

Cycles 2, 3, 4, 5 & 6 Day 8

18. Vincristine 1.4mg/m² (max 2mg) intravenous bolus in 50ml sodium chloride 0.9% over 10 minutes

19. Bleomycin 10,000 international units/m² intravenous bolus over 10 minutes

20. Hydrocortisone 100mg intravenous when required for the treatment of bleomycin related reactions

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1	June 2019	None	Rebecca Wills Pharmacist Dr Debbie Wright Pharmacist	Dr Robert Lown 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 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.