Chemotherapy Protocol

LYMPHOMA
BRENTUXIMAB VEDOTIN-CYCLOPHOSPHAMIDE-DOXORUBICIN-PREDNISOLONE
(BV-CHP)

Regimen

- Lymphoma – Brentuximab vedotin-cyclophosphamide-doxorubicin-prednisolone

Indication

Brentuximab vedotin in combination with cyclophosphamide, doxorubicin and prednisolone for previously untreated systemic anaplastic large cell lymphoma (sALCL) in an ADULT patient where the following criteria is met:

- The patient has a proven histological diagnosis of CD30+ve systemic anaplastic large cell lymphoma (sALCL)
- The patient is previously untreated for systemic anaplastic large cell lymphoma
- The patient has not received prior treatment with brentuximab vedotin
- The patient will be treated with brentuximab vedotin in combination with cyclophosphamide, doxorubicin and prednisolone
- The patient will be treated with a maximum of 6 or 8 cycles of chemotherapy (6 cycles being the usual maximum)
- The patient has an ECOG performance status of 0, 1 or 2

Toxicity

Drug	Adverse Effect
Brentuximab Vedotin	Peripheral sensory neuropathy, cough, diarrhoea, infusion related reactions, upper respiratory tract infections, progressive multifocal leukoencephalopathy
Cyclophosphamide	Dysuria, haemorrhagic cystitis (rare), taste disturbances
Doxorubicin	Cardiomyopathy, alopecia, urinary discolouration (red)
Prednisolone	Weight gain, gastro-intestinal disturbances, hyperglycaemia, CNS disturbances, cushingoid changes, glucose intolerance

The adverse effects listed are not exhaustive. Please refer to the relevant summary of product characteristics for further details.

Monitoring

- FBC U&E (including magnesium and calcium), glucose and LFTs prior to each cycle
- 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.

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.

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

Prior to prescribing on day one of each cycle the following criteria must be met;

Criteria	Eligible level
Neutrophil	equal to or more than $1.0x10^9$/L
Platelet	equal to or more than $75x10^9$/L

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

Hepatic Impairment

Drug	**Bilirubin (µmol)**		**AST/ALT (units/L)**	**Dose (% of original dose)**
Cyclophosphamide	No dose adjustment 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

Drug	Child-Pugh score	Dose (% original dose)
Brentuximab vedotin*	A	The recommended starting dose in patients with hepatic impairment is 1.2 mg/kg. Patients with hepatic impairment should be closely monitored for adverse events
	B or C	Not recommended

*There is no clinical trial experience using Brentuximab vedotin in combination with chemotherapy in patients with hepatic impairment, where total bilirubin is > 1.5 times the upper limit of normal (ULN) (unless due to Gilbert syndrome), or aspartate aminotransferase (AST) or alanine aminotransferase (ALT) are > 3 times the ULN, or > 5 times the ULN if their elevation may be reasonably ascribed to the presence of HL in the liver. Use of Brentuximab

vedotin in combination with chemotherapy should be avoided in patients with moderate and severe hepatic impairment.

Renal Impairment

Drug	Creatinine clearance (ml/min)	Dose (% of original dose)
Cyclophosphamide*	More than 20	100%
	10-20	75%
	Less than 10	50%
Doxorubicin	Less than 10	75%
Brentuximab vedotin**	Less than 30	The recommended starting dose in patients with severe renal impairment is 1.2 mg/kg. Patients with renal impairment should be closely monitored for adverse events

*Consider mesna in patients with pre-existing bladder disorders. Give an oral dose of 40% of the cyclophosphamide dose (rounded upwards to the nearest 400mg) at 0, 2 and 6 hours after the administration of the cyclophosphamide.

** There is no clinical trial experience using Brentuximab vedotin in combination with chemotherapy in patients with renal impairment, where serum creatinine is ≥ 2.0 mg/dL and/or creatinine clearance or calculated creatinine clearance is ≤ 40 mL/minute. Use of Brentuximab vedotin in combination with chemotherapy should be avoided in patients with severe renal impairment.

Other

Brentuximab Vedotin
Skin

Cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis have been reported in patients who received brentuximab vedotin. If patients experience any skin reactions during treatment, they should be monitored closely and, in the case of any suspicion of the skin reaction evolving to a serious muco-cutaneous reaction, treatment with brentuximab vedotin should be withheld until complete resolution of the event or discontinued. Other potential causes of skin toxicity should be evaluated and suspected agents discontinued accordingly.

Lung

The concomitant use of bleomycin is contra-indicated because of the increased risk of pulmonary toxicity

Peripheral Neuropathy

Severity of peripheral sensory or motor neuropathy	Modification of dose and schedule
Grade 1 (paraesthesia and/or loss of reflexes, with no loss of function)	Continue with the same dose and schedule.
Grade 2 (interfering with function but not with activities of daily living)	Sensory neuropathy: Continue treatment at same dose level. Motor neuropathy: Reduce dose to 1.2 mg/kg, up to a maximum of 120 mg every 3 weeks.
Grade 3 (interfering with activities of daily living)	Sensory neuropathy: Reduce dose to 1.2 mg/kg up to a maximum of 120 mg every 3 weeks. Motor neuropathy: Discontinue treatment.
Grade 4 (sensory neuropathy which is disabling or motor neuropathy that is life-threatening or leads to paralysis)	Discontinue treatment.

Infusion reactions

Infusion related adverse reactions, including anaphylaxis, have been observed in patients treated with brentuximab vedotin. If anaphylaxis occurs, immediately and permanently discontinue brentuximab vedotin and administer appropriate medical therapy.

For other infusion related reactions including chills, nausea, dyspnoea, pruritus, pyrexia and cough interrupt the infusion and institute appropriate medical management. Give pre-medication consisting of chlorphenamine, hydrocortisone and paracetamol for all subsequent infusions. The infusion may be restarted at a slower rate after symptom resolution.

Progressive multifocal leukoencephalopathy

Use of brentuximab vedotin has been associated with an increased risk of progressive multifocal leukoencephalopathy (PML). Patients must be monitored at regular intervals for any new or worsening neurological, cognitive or psychiatric symptoms that may be suggestive of PML. If PML is suspected, further dosing must be suspended until PML has been excluded. If PML is confirmed the brentuximab must be permanently discontinued.

Doxorubicin

Discontinue if cardiac failure develops.

Regimen

21 day cycle for up to 8 cycles (6 cycles set on aria)

Drug	Dose	Days	Administration
Brentuximab Vedotin	1.8mg/kg (maximum 180mg)	1	Intravenous infusion in 250ml sodium chloride 0.9% over 30 minutes

Cyclophosphamide	750mg/m^2	1	Intravenous bolus over 10 minutes
Doxorubicin	50mg/m^2	1	Intravenous bolus over 10 minutes
Prednisolone	100mg once a day	1, 2, 3, 4, 5	Oral

Dose Information

- Brentuximab vedotin will be dose banded according to the national dose bands 50mg/10ml)
- The dose of brentuximab vedotin will be capped at 180mg
- Cyclophosphamide will be dose banded in accordance with national dose bands (20PM)
- Doxorubicin will be dose banded in accordance with national dose bands (2pm)
- 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

Administration Information

- Brentuximab vedotin should be administered through a dedicated intravenous line and it must not be mixed with other medicinal products

Extravasation

- Brentuximab vedotin – neutral
- Cyclophosphamide – neutral
- Doxorubicin – vesicant

Other

- Brentuximab doses below 100mg should be diluted in 100ml sodium chloride 0.9%.
- Prednisolone should be taken in the morning with or after food.

Additional Therapy

- Antiemetics

15-30 minutes before chemotherapy on day one only;
- ondansetron 8mg oral or intravenous

As take home medication
- metoclopramide 10mg three times a day oral when required

- ondansetron 8mg twice a day oral for 3 days

- When required for the relief of Brentuximab vedotin infusion related reactions:

    - Chlorphenamine 10mg intravenous
    - Hydrocortisone 100mg intravenous
    - Paracetamol 1000mg oral
    - Salbutamol 2.5mg nebule

- Allopurinol 300mg once a day for first cycle only

- Growth factors For example:
  - filgrastim or bioequivalent 30 million units once a day from day 6 for 7 days subcutaneous
  - lenograstim or bioequivalent 33.6 million units once a day from day 6 for 7 days subcutaneous
  - pegfilgrastim or bioequivalent 6mg once only on day 2 subcutaneous

- Anti-infective prophylaxis
  - aciclovir 400mg twice a day oral
  - co-trimoxazole 960mg once a day on Monday, Wednesday and Friday only oral

- Loperamide 4mg initially then 2mg after each loose stool when required for diarrhoea.

- 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.

- Mouthwashes according to local or national policy on the treatment of mucositis

Additional information

- Brentuximab is metabolised by CYP3A isoenzyme. Always check for interactions.

References

1. Sandoz Limited. Cyclophosphamide 1000mg powder for solution for injection or infusion summary of product characteristics. Available from: https://www.medicines.org.uk/emc/product/3525/smpc. Last updated 06/04/2021. Accessed 17/10/2022.
2. Accord Healthcare limited. Doxorubicin 2mg/ml concentrate for solution for infusion summary of product characteristics. Available from: https://www.medicines.org.uk/emc/product/6112/smpc. Last updated 02/06/2016. Accessed 17/10/2022.
3. Takeda UK Ltd. Adcetris 50mg powder for concentrate for solution for infusion summary of product characteristics. Available from: https://www.medicines.org.uk/emc/product/2859/smpc. Last updated 08/06/2022. Accessed 17/10/2022.
4. Horwitz, S., O. A. O'Connor, B. Pro, et al. 2019. "Brentuximab vedotin with chemotherapy for CD30- positive peripheral T-cell lymphoma (ECHELON-2): a global, double-blind, randomised, phase 3 trial." Lancet 393(10168):229-240.

REGIMEN SUMMARY

Brentuximab vedotin-Cyclophosphamide-Doxorubicin-Prednisolone (BV-CHP)

Cycle 1 Day 1

1. Ondansetron 8mg oral
Administration instructions:
Administer 15-30 minutes prior to chemotherapy. This may be given as ondansetron 8mg IV stat or equivalent.

2. Brentuximab vedotin 1.8mg/kg (max 180mg) intravenous infusion in 250ml sodium chloride 0.9% over 30 minutes
Administration instructions:
Doses below 100mg should be diluted in 100ml sodium chloride 0.9%.

3. Doxorubicin 50mg/m^2 intravenous bolus over 10 minutes.

4. Cyclophosphamide 750mg/m^2 intravenous bolus over 10 minutes

5. Chlorphenamine 10mg intravenous when required for the treatment of brentuximab vedotin infusion related reactions
Administration instructions:
When required for the treatment of brentuximab vedotin infusion related reactions.

6. Hydrocortisone 100mg intravenous when required for the treatment of brentuximab vedotin infusion related reactions
Administration instructions:
When required for the treatment of brentuximab vedotin infusion related reactions.

7. Paracetamol 1000mg oral when required for the treatment of brentuximab vedotin infusion related reactions
Administration instructions:
When required for the treatment of brentuximab vedotin infusion related reactions.

8. Salbutamol 2.5mg nebule when required for the relief of brentuximab vedotin related bronchospasm
Administration instructions:
When required for the treatment of brentuximab vedotin infusion related bronchospasm.

Take Home Medicines

8. Prednisolone 100mg once a day on the morning of the next treatment **
Administration instructions:
To be taken on the morning of the next treatment, with or after food.
Prednisolone may be dispensed as a single supply in one container or as two containers according to local practice.

9. Prednisolone 100mg once a day for 4 days oral (starting on day 2)**
Administration instructions:
To be taken in the mornings, with or after food starting on day two of the cycle.
Prednisolone may be dispensed as a single supply in one container or as two containers according to local practice.

10. Metoclopramide 10mg three times a day when required oral
Administration instructions:
When required for the relief of nausea. Please supply 5 days or an original pack if appropriate.

11. Ondansetron 8mg twice a day for 3 days starting on the evening of day 1 of the cycle oral

Administration instructions:
To start on the evening of day one of the cycle.

12. Allopurinol 300mg once a day oral for 21 days oral

Administration instructions:
Take with or after food with plenty of water. Please supply 21 days or an original pack if appropriate.

13. Aciclovir 400mg Twice a day for 21 days oral

Administration instructions:
Please supply 21 days or an original pack if appropriate

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

Administration instructions:
This may be given as 480mg twice a day on Mondays, Wednesdays and Fridays according to local practice.

15. Growth factors For example:

Administration instructions:
Growth factors according to local formulary. For example:

- filgrastim or bioequivalent 30 million units once a day from day 6 for 7 days subcutaneous
- lenograstim or bioequivalent 33.6 million units once a day from day 6 for 7 days subcutaneous
- pegfilgrastim or bioequivalent 6mg once only on day 2 subcutaneous

Cycle 2, 3, 4, 5 day 1

16. Ondansetron 8mg oral

Administration instructions:
Administer 15-30 minutes prior to chemotherapy. This may be given as ondansetron 8mg IV stat or equivalent.

17. Brentuximab vedotin 1.8mg/kg (max 180mg) intravenous infusion in 250ml sodium chloride 0.9% over 30 minutes

Administration instructions:
Doses below 100mg should be diluted in 100ml sodium chloride 0.9%.

18. Doxorubicin 50mg/m^2 intravenous bolus over 10 minutes.

19. Cyclophosphamide 750mg/m^2 intravenous bolus over 10 minutes

20. Chlorphenamine 10mg intravenous when required for the treatment of brentuximab vedotin infusion related reactions

Administration instructions:
When required for the treatment of brentuximab vedotin infusion related reactions.

21. Hydrocortisone 100mg intravenous when required for the treatment of brentuximab vedotin infusion related reactions

Administration instructions:
When required for the treatment of brentuximab vedotin infusion related reactions.

22. Paracetamol 1000mg oral when required for the treatment of brentuximab vedotin infusion related reactions

Administration instructions:
When required for the treatment of brentuximab vedotin infusion related reactions.

23. Salbutamol 2.5mg nebule when required for the relief of brentuximab vedotin related bronchospasm

Administration instructions:
When required for the treatment of brentuximab vedotin infusion related reactions.

Take Home Medicines

8. Prednisolone 100mg once a day on the morning of the next treatment **
Administration instructions:
To be taken on the morning of the next treatment, with or after food.
Prednisolone may be dispensed as a single supply in one container or as two containers according to local practice.

9. Prednisolone 100mg once a day for 4 days oral (starting on day 2)**
Administration instructions:
To be taken in the mornings, with or after food starting on day two of the cycle.
Prednisolone may be dispensed as a single supply in one container or as two containers according to local practice.

10. Metoclopramide 10mg three times a day when required oral
Administration instructions:
When required for the relief of nausea. Please supply 5 days or an original pack if appropriate.

24. Ondansetron 8mg twice a day for 3 days starting on the evening of day 1 of the cycle oral
Administration instructions:
To start on the evening of day one of the cycle.

25. Aciclovir 400mg Twice a day for 21 days oral
Administration instructions:
Please supply 21 days or an original pack if appropriate

26. Co-trimoxazole 960mg once a day on Monday, Wednesday and Friday for 21 days oral
Administration instructions:
This may be given as 480mg twice a day on Mondays, Wednesdays and Fridays according to local practice.

27. Growth factors For example:
Administration instructions:
Growth factors according to local formulary. For example:
- filgrastim or bioequivalent 30 million units once a day from day 6 for 7 days subcutaneous
- lenograstim or bioequivalent 33.6 million units once a day from day 6 for 7 days subcutaneous
- pegfilgrastim or bioequivalent 6mg once only on day 2 subcutaneous

Cycle 6 day 1

28. Ondansetron 8mg oral
Administration instructions:
Administer 15-30 minutes prior to chemotherapy. This may be given as ondansetron 8mg IV stat or equivalent.

29. Brentuximab vedotin 1.8mg/kg (max 180mg) intravenous infusion in 250ml sodium chloride 0.9% over 30 minutes
Administration instructions:
Doses below 100mg should be diluted in 100ml sodium chloride 0.9%.

30. Doxorubicin 50mg/m^2 intravenous bolus over 10 minutes.

31. Cyclophosphamide 750mg/m^2 intravenous bolus over 10 minutes

32. Chlorphenamine 10mg intravenous when required for the treatment of brentuximab vedotin infusion related reactions
Administration instructions:
When required for the treatment of brentuximab vedotin infusion related reactions.

33. Hydrocortisone 100mg intravenous when required for the treatment of brentuximab vedotin infusion related reactions
Administration instructions:
When required for the treatment of brentuximab vedotin infusion related reactions.

34. Paracetamol 1000mg oral when required for the treatment of brentuximab vedotin infusion related reactions
Administration instructions:

When required for the treatment of brentuximab vedotin infusion related reactions.

35. Salbutamol 2.5mg nebule when required for the relief of brentuximab vedotin related bronchospasm

Administration instructions:
When required for the treatment of brentuximab vedotin infusion related reactions.

Take Home Medicines

36. Prednisolone 100mg once a day for 4 days oral (starting on day 2)**

Administration instructions:
To be taken in the mornings, with or after food starting on day two of the cycle.
Prednisolone may be dispensed as a single supply in one container or as two containers according to local practice.

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

Administration instructions:
When required for the relief of nausea. Please supply 5 days or an original pack if appropriate.

38. Ondansetron 8mg twice a day for 3 days starting on the evening of day 1 of the cycle oral

Administration instructions:
To start on the evening of day one of the cycle.

39. Aciclovir 400mg Twice a day for 21 days oral

Administration instructions:
Please supply 21 days or an original pack if appropriate

40. Co-trimoxazole 960mg once a day on Monday, Wednesday and Friday oral

Administration instructions:
This may be given as 480mg twice a day on Mondays, Wednesdays and Fridays according to local practice.

41. Growth factors For example:

Administration instructions:
Growth factors according to local formulary. For example:

- filgrastim or bioequivalent 30 million units once a day from day 6 for 7 days subcutaneous
- lenograstim or bioequivalent 33.6 million units once a day from day 6 for 7 days subcutaneous
- pegfilgrastim or bioequivalent 6mg once only on day 2 subcutaneous

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1	December 2022	None	Alexandra Pritchard Pharmacist	Dr Rob Lown Consultant Haematologist

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 that occur as a result of following these guidelines.