Chemotherapy Protocol

LYMPHOMA

REPOCH - CYCLOPHOSPHAMIDE-DOXORUBICIN-ETOPOSIDE-PREDNISOLONE-RITUXIMAB-VINCRISTINE

(Dose adjusted regimen)

There are multiple versions of this protocol in use. Please ensure you have the correct protocol for the relevant diagnosis and place of administration.

Regimen

- Lymphoma – REPOCH (dose adjusted)-Cyclophosphamide-Doxorubicin-Etoposide-Prednisolone-Rituximab-Vincristine

Indication

- CD20 positive Non-Hodgkin's Lymphoma

Toxicity

Drug	Adverse Effect
Cyclophosphamide	Dysuria, haemorrhagic cystitis (rare), taste disturbances
Doxorubicin	Cardiomyopathy, alopecia, urinary discolouration (red),
Etoposide	Hypotension on rapid infusion, alopecia, hyperbilirubinaemia
Prednisolone	Weight gain, gastro-intestinal disturbances, hyperglycaemia, CNS disturbances, cushingoid changes, glucose intolerance
Rituxumab	Severe cytokine release syndrome, increased incidence of infective complications, progressive multifocal leukoencephalopathy
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.

Monitoring

Drugs

- FBC, LFTs (including albumin) and U&Es prior to day one of treatment
- Regular blood glucose monitoring
- Check hepatitis B status before starting rituximab
- 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

Dose Modifications

The dose modifications listed are for haematological, liver and renal function and limited drug specific toxicities. 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 in the table 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.

Consider blood transfusion if patient symptomatic of anaemia or has a haemoglobin of less than 8g/dL (80g/L).

EPOCH dose-adjustment paradigm

Please note that dose adjustments from cycle two onwards apply to the whole treatment cycle and are based on the neutrophil and/or platelet count at the nadir of the previous cycle. This is monitored by obtaining twice weekly FBC, i.e. days 9, 12, 15 and 18.

Doses should be based on actual body weight and should not be routinely capped. This includes vincristine. ARIA automatically caps doses at 2.4m^2. Doses may have to be manually adjusted to compensate for this.

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

Neutrophils (x10^9/L) at Nadir	**Dose Modifications (cyclophosphamide, doxorubicin and etoposide)**
Greater or equal to 0.5	Increase doses by 1 level*
Less than 0.5 on 1 or 2 measurements	Maintain doses at the same level as the previous cycle
Less than 0.5 on 3 or more measurements	Decrease doses by 1 level
Platelets (x10^9/L) at Nadir	**Dose Modifications (cyclophosphamide, doxorubicin and etoposide)**
Less than 25 on 1 measurement	Decrease doses by 1 level

Dose Level	**Cyclophosphamide mg/m^2**	**Doxorubicin mg/m^2**	**Etoposide mg/m^2**
3	1100	14	70
2	900	12	60
1	750	10	50
-1	600	8	40
-2	500	6	30

*Please note where doses have been previously been reduced below level 1 any subsequent dose escalations apply to cyclophosphamide only.

Hepatic Impairment

Please note that the approach may be different where abnormal liver function tests are due to disease involvement.

Drug	Bilirubin (µmol/L)		AST/ALT (units)	Dose (%of original dose)
Cyclophosphamide	more than 30	or	2-3xULN	Clinical decision. Evidence that exposure to active metabolites may not be increased, suggesting dose reduction may not be 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	Consider dose reducing to 50%
	more than 51	or	More than180	Clinical decision
Rituximab	N/A		N/A	No dose adjustment needed
Vincristine	30-51	or	60-180	50%
	more than 51	and	normal	50%
	more than 51	and	more than 180	omit

Renal Impairment

Drug	Creatinine Clearance (ml/min)	Dose (% of original dose)
Cyclophosphamide*	more than 20	100%
	10-20	75%
	less than 10	omit
Doxorubicin	less than 10	Consider dose reduction in severe renal failure
Etoposide	more than 50	100%
	15-50	75%
	Less than15	50%
Rituximab	N/A	No dose adjustment needed
Vincristine	N/A	No dose adjustment needed

*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.

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.

Doxorubicin

Discontinue doxorubicin if cardiac failure develops

Etoposide

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

Rituximab

Infusion related adverse reactions have been observed in 10% of patients treated with rituximab.

Rituximab administration is associated with the onset of cytokine release syndrome. This condition is characterised by severe dyspnoea, often accompanied by bronchospasm and hypoxia, in addition to fever, chills, rigors, urticaria, and angioedema. It may be associated with some features of tumour lysis syndrome such as hyperuricaemia, hyperkalaemia, hypocalcaemia, acute renal failure, elevated lactate dehydrogenase (LDH) and can lead to acute respiratory failure and death. This effect on the lungs may be accompanied by events such as pulmonary interstitial infiltration or oedema, visible on a chest x-ray.

Cytokine release syndrome frequently occurs within one or two hours of initiating the first infusion.

Hypersensitivity reactions, including anaphylaxis, have been reported following the intravenous administration of proteins. In contrast to cytokine release syndrome, true hypersensitivity reactions typically occur within minutes of starting the infusion. Medicinal products for the treatment of allergic reactions should be available for immediate use in the event of hypersensitivity developing during the administration of rituximab.

Use of rituximab maybe 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 rituximab must be permanently discontinued.

The presence of a viral upper respiratory tract infection at the time of treatment may increase the risk of rituximab associated hepatotoxicity. Patients should be assessed for any cold or flu-like symptoms prior to treatment

Vincristine

Reduce the vincristine dose by 25% for a NCI-CTC grade 2 motor neuropathy or by 50% for a grade 3 motor or sensory neurological toxicity. For higher toxicity grades, or if toxicity increases despite dose reduction stop the vincristine.

Regimen

21 day cycle for 6 cycles

Dose Level 1 will be used as the default on ARIA

Drug	Dose	Days	Administration
Rituximab	375mg/m^2	1	Intravenous infusion in 500ml sodium chloride 0.9%
Doxorubicin	20mg/m^2	1, 3	Continuous intravenous infusion in 1000ml sodium chloride 0.9% over 48 hours
Etoposide	100mg/m^2	1, 3	
Vincristine	0.8mg/m^2	1, 3	
Cyclophosphamide	750mg/m^2	5	Intravenous bolus over 10 minutes
Prednisolone	100mg	1, 2, 3, 4, 5	Oral

Dose Information

- Cyclophosphamide will be dose banded in accordance with the national dose bands (20mg/ml)
- Doxorubicin will be dose banded in accordance with the national dose bands (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 will be dose banded in accordance with the national bands (20mg/ml)

- Rituximab dose will be rounded to the nearest 100mg (up if halfway)

- Vincristine dose will be dose banded in accordance with the national bands (1mg/ml)

- Doses should be based on actual body weight and should not be routinely capped. This includes vincristine. ARIA automatically caps doses at 2.4m^2. Doses may have to be manually adjusted to compensate for this.

Administration Information

Extravasation

- Cyclophosphamide – neutral

- Doxorubicin – vesicant

- Etoposide - irritant

- Rituximab - neutral

- Vincristine - vesicant

Other

- Prednisolone should be taken in the morning with or after food. Administration of prednisolone begins on the morning of chemotherapy.

- The rate of administration of rituximab varies. Please refer to the rituximab administration guidelines.

- This regimen involves the administration of vesicants as a continuous infusion. Patients should have a PICC line or central access in place.

Additional Therapy

- Antiemetics

  Starting 15-30 minutes prior to chemotherapy

  - ondansetron 8mg twice a day for 5 days oral or intravenous
  - metoclopramide 10mg three times a day when required oral

- Rituximab pre-medication

  30 minutes prior to rituximab

  - chlorphenamine 10mg intravenous

- paracetamol 1000mg oral

On the morning of treatment

- prednisolone 100mg oral to be self administered by the patient on the morning of treatment and for four days after rituximab treatment (this is part of the chemotherapy schedule as well as rituximab pre-medication)

- Rituximab infusion reactions

  - hydrocortisone 100mg intravenous when required for rituximab infusion related reactions
  - salbutamol 2.5mg nebule when required for rituximab related bronchospasm
  - consider pethidine 25-50mg intravenous bolus for rituximab related rigors that fail to respond to steroids.

- Allopurinol 300mg once a day for seven days oral for the first cycle only

- Growth factor to be started on day 6 of the treatment cycle and continued until the neutrophil count is above $5x10^9$/L (10 doses supplied). For example

  - filgrastim or bioequivalent 30million units (300microgram) once a day subcutaneous
  - lenograstim or bioequivalent 13.4million units (263microgram) once a day subcutaneous
  - pegfilgrastim or bioequivalent 6mg once only subcutaneous

- Anti-infective prophylaxis as follows:

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

- Mouthcare for the prophylaxis or treatment of mucositis in accordance with local guidelines

- 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.

Additional Information

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

Coding

- Procurement – X70.8

- Delivery – X72.9

References
1. Jermann M, Jost, L, Taverna C *et al.*; Rituximab–EPOCH, an effective salvage therapy for relapsed, refractory or transformed B-cell lymphomas: results of a phase II study; Annals of Oncology 15; 511–516: 2004

REGIMEN SUMMARY

REPOCH (dose adjusted)-Cyclophosphamide-Doxorubicin-Etoposide-Prednisolone-Rituximab-Vincristine

Cycle 1

Day 1

1. Warning – Do not cap doses
   Administration Instructions
   Doses should be based on actual body weight and should not be routinely capped. This includes vincristine. ARIA automatically caps doses at 2.4m^2. Doses may have to be manually adjusted to compensate for this.

2. Prednisolone 100mg oral
   Administration instructions
   Take with or after food.

3. Chlorphenamine 10mg intravenous

4. Paracetamol 1000mg oral
   Administration Instructions
   Please check if the patient has taken paracetamol. Maximum dose is 4g per 24 hours. There should be 4 hours between doses.

5. Rituximab 375mg/m^2 intravenous infusion in 500ml sodium chloride 0.9% as per the rituximab administration guidelines

6. Ondansetron 8mg oral or intravenous

7. Warning – Combination Bag
   Administration Instructions
   The doxorubicin, etoposide and vincristine are mixed in the same infusion bag of 1000ml sodium chloride 0.9% and administered over 48 hours. To prevent separate bags from being made and administered only the doxorubicin will have a volume and rate of administration on ARIA.

8. Doxorubicin 20mg/m^2 plus etoposide 100mg/m^2 plus vincristine 0.8mg/m^2 continuous intravenous infusion in sodium chloride 0.9% 1000ml over 48hours
   Administration Instructions
   The doxorubicin, etoposide and vincristine are mixed in the same infusion bag of 1000ml sodium chloride 0.9% and administered over 48 hours. To prevent separate bags from being made and administered only the doxorubicin will have a volume and rate of administration on ARIA.

9. Hydrocortisone 100mg intravenous bolus once only when required for the relief of rituximab infusion related reactions

10. Salbutamol 2.5mg nebule once only when required for the relief of rituximab related bronchospasm

Day 3

11. Warning – Check Supportive Medicines
    Administration Instructions
    Please check the patient has taken on the morning of treatment;
    - prednisolone 100mg oral
    - ondansetron 8mg oral

    If the patient has not taken these medicines please administer to the patient

12. Warning – Combination Bag
    Administration Instructions
    The doxorubicin, etoposide and vincristine are mixed in the same infusion bag of 1000ml sodium chloride 0.9% and administered over 48 hours. To prevent separate bags from being made and administered only the doxorubicin will have a volume and rate of administration on ARIA.

13. Doxorubicin 20mg/m^2 plus etoposide 100mg/m^2 plus vincristine 0.8mg/m^2 continuous intravenous infusion in sodium chloride 0.9% 1000ml over 48 hours
    Administration Instructions
    The doxorubicin, etoposide and vincristine are mixed in the same infusion bag of 1000ml sodium chloride 0.9% and administered over 48 hours. To prevent separate bags from being made and administered only the doxorubicin will have a volume and rate of administration on ARIA.

Day 5

14. Warning – Check Supportive Medicines
    Administration Instructions
    Please check the patient has taken on the morning of treatment;
    - prednisolone 100mg oral
    - ondansetron 8mg oral

    If the patient has not taken these medicines please administer to the patient.

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

Take Home Medicines (day 1 only)

16. Prednisolone 100mg once a day for four days starting on day two of the cycle
    Administration Instructions
    Take in the morning with or after food starting on day 2 of the cycle for four days

17. Ondansetron 8mg twice a day starting on the evening of day one of the cycle for 5 days oral
    Administration Instructions
    Take 8mg twice a day starting on the evening of day 1 of the cycle.

18. Metoclopramide 10mg three times a day when required for the relief of nausea oral
    Administration Instructions
    Please supply 21 days or the nearest original pack size.

19. Aciclovir 400mg twice a day for 21 days oral

20. Co-trimoxazole 960mg each morning on Monday, Wednesday and Friday only for 21 days

21. Allopurinol 300mg once a day for 7 days oral

22. Growth Factors according to local formulary choice
    Administration Instructions
    Growth factor to be started on day 6 of the treatment cycle and continued until the neutrophil count is above 5x10^9/L.
    For example;

    - filgrastim or bioequivalent 30 million units (300microgram) once a day subcutaneous (supply 10 doses)
    - lenograstim or bioequivalent 13.4 million units (263microgram) once a day subcutaneous (supply 10 doses)
    - pegfilgrastim or bioequivalent 6mg once only subcutaneous (supply 1 dose)

Cycles 2, 3, 4, 5 & 6

Day 1

23. Warning – Check dose adjustments and cap
Administration Instructions
Dose adjustments from cycle two onwards apply to the whole treatment cycle and are based on the neutrophil and/or platelet count at the nadir of the previous cycle. This is monitored by obtaining twice weekly FBC, i.e. days 9, 12, 15 and 18.

Dose modifications based on haematological parameters apply to cyclophosphamide, doxorubicin and etoposide only. Refer to the protocol for details of dose adjustments.

Doses should be based on actual body weight and should not be routinely capped. This includes vincristine. ARIA automatically caps doses at 2.4m^2. Doses may have to be manually adjusted to compensate for this.

24. Prednisolone 100mg oral
Administration instructions
Take with or after food.

25. Chlorphenamine 10mg intravenous

26. Paracetamol 1000mg oral
Administration Instructions
Please check if the patient has taken paracetamol. Maximum dose is 4g per 24 hours. There should be 4 hours between doses.

27. Rituximab 375mg/m^2 intravenous infusion in 500ml sodium chloride 0.9% as per the rituximab administration guidelines

28. Ondansetron 8mg oral or intravenous

29. Warning – Combination Bag
Administration Instructions
The doxorubicin, etoposide and vincristine are mixed in the same infusion bag of 1000ml sodium chloride 0.9% and administered over 48 hours. To prevent separate bags from being made and administered only the doxorubicin will have a volume and rate of administration on ARIA.

30. Doxorubicin 20mg/m^2 plus etoposide 100mg/m^2 plus vincristine 0.8mg/m^2 continuous intravenous infusion in sodium chloride 0.9% 1000ml over 48hours
Administration Instructions
The doxorubicin, etoposide and vincristine are mixed in the same infusion bag of 1000ml sodium chloride 0.9% and administered over 48 hours. To prevent separate bags from being made and administered only the doxorubicin will have a volume and rate of administration on ARIA.

31. Hydrocortisone 100mg intravenous bolus once only when required for the relief of rituximab infusion related reactions

32. Salbutamol 2.5mg nebule once only when required for the relief of rituximab related bronchospasm

Day 3

33. Warning – Check Supportive Medicines
Administration Instructions
Please check the patient has taken on the morning of treatment;
- prednisolone 100mg oral
- ondansetron 8mg oral

If the patient has not taken these medicines please administer to the patient

34. Warning – Combination Bag
    Administration Instructions
    The doxorubicin, etoposide and vincristine are mixed in the same infusion bag of 1000ml sodium chloride 0.9% and administered over 48 hours. To prevent separate bags from being made and administered only the doxorubicin will have a volume and rate of administration on ARIA.

35. Doxorubicin 20mg/m^2 plus etoposide 100mg/m^2 plus vincristine 0.8mg/m^2 continuous intravenous infusion in sodium chloride 0.9% 1000ml over 48hours
    Administration Instructions
    The doxorubicin, etoposide and vincristine are mixed in the same infusion bag of 1000ml sodium chloride 0.9% and administered over 48 hours. To prevent separate bags from being made and administered only the doxorubicin will have a volume and rate of administration on ARIA.

Day 5

36. Warning – Check Supportive Medicines
    Administration Instructions
    Please check the patient has taken on the morning of treatment;
    - prednisolone 100mg oral
    - ondansetron 8mg oral

    If the patient has not taken these medicines please administer to the patient.

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

Take Home Medicines (day 1 only)

38. Prednisolone 100mg once a day for four days starting on day two of the cycle
    Administration Instructions
    Take in the morning with or after food starting on day 2 of the cycle for four days

39. Ondansetron 8mg twice a day starting on the evening of day one of the cycle for 5 days oral
    Administration Instructions
    Take 8mg twice a day starting on the evening of day 1 of the cycle.

40. Metoclopramide 10mg three times a day when required for the relief of nausea oral
    Administration Instructions
    Please supply 21 days or the nearest original pack size.

41. Aciclovir 400mg twice a day for 21 days oral

42. Co-trimoxazole 960mg each morning on Monday, Wednesday and Friday only for 21 days

43. Growth Factors according to local formulary choice
    Administration Instructions
    Growth factor to be started on day 6 of the treatment cycle and continued until the neutrophil count is above $5x10^9$/L.
    For example;

    - filgrastim or bioequivalent 30 million units (300microgram) once a day subcutaneous (supply 10 doses)
    - lenograstim or bioequivalent 13.4 million units (263microgram) once a day subcutaneous (supply 10 doses)
    - pegfilgrastim or bioequivalent 6mg once only subcutaneous (supply 1 dose)

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1.1	August 2018	Metoclopramide Dose Change to 10mg. Vincristine dose reductions Combination bag over 48 hours. Warnings added to summary Disclaimer updated	Dr Deborah Wright Pharmacist	Dr Rob Lown Consultant Haematologist
1	August 2012	None	Dr Deborah Wright Pharmacist	Dr Andrew Davies Consultant Medical Oncologist Dr Alison Milne 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 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 that occur as a result of following these guidelines. These protocols should be used in conjunction with other references such as the Summary of Product Characteristics and relevant published papers.