Chemotherapy Protocol

LYMPHOMA

CYCLOPHOSPHAMIDE-DOXORUBICIN-PREDNISOLONE-RITUXIMAB-VINCRISTINE (mini-RCHOP 21)

Regimen

- Lymphoma – mini-RCHOP (21)-Cyclophosphamide-Doxorubicin-Prednisolone-Rituximab-Vincristine

Indication

- CD20 positive Non-Hodgkin's Lymphoma
- Patients over 80 years old or with significant other co-morbidities and unlikely to tolerate full dose RCHOP.

Toxicity

Drug	Adverse Effect
Cyclophosphamide	Dysuria, haemorrhagic cystitis (rare), taste disturbances, myelosuppression, neutropenia, leukopenia, mucositis, alopecia, fever
Doxorubicin	Cardiomyopathy, alopecia, urinary discolouration (red), infections, bone-marrow suppression, leucopenia, neutropenia, anorexia, nausea, vomiting, mucositis, stomatitis, diarrhoea, alopecia.
Prednisolone	Weight gain, gastro-intestinal disturbances, hyperglycaemia, infection, Cushing-like symptoms, hypokalaemia, sodium retention, osteoporosis, impaired wound healing, muscular atrophy, osteoporosis,
Rituxumab	Severe cytokine release syndrome, increased incidence of infective complications, progressive multifocal leukoencephalopathy, neutropenia, infusion related reactions, angioedema, nausea, pruritus, rash, alopecia, fever, chills, asthenia, headache, decreased IgG levels.
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 and U&Es prior to day one of treatment
- 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.

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

Neutrophils (x10^9/L)	Dose Modifications
Less than 1 on proposed day 1 of cycle	Delay therapy until neutrophils are greater than or equal to 1x10^9/L Consider G-CSF as secondary prophylaxis. Reconsider treatment options if not recovered after 14 days
Grade 4 neutropenia leading to infection despite G-CSF support	Reduce dose of cyclophosphamide and doxorubicin by 50% for all subsequent cycles
Grade 4 neutropenia recurs despite 50% dose reduction in cyclophosphamide and doxorubicin	Stop treatment
Platelets (x10^9/L)	**Dose Modifications (cyclophosphamide and doxorubicin)**
Less than 100 on proposed day 1 of cycle	Delay therapy until platelets are greater or equal to 100x10^9/L Reconsider treatment options if not recovered after 14 days
Grade 4 thrombocytopenia following any cycle	Reduce dose of cyclophosphamide and doxorubicin by 50% for all subsequent cycles
Grade 4 thrombocytopenia recurs despite 50% dose reduction in cyclophosphamide and doxorubicin	Stop treatment

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		2-3xULN	Clinical decision. Evidence that exposure to active metabolites may not be increased, suggesting dose reduction may not be necessary. There may be decreased efficacy in severe hepatic impairment.
Doxorubicin	Equal or less than 20	and	2-3xULN	75%

	20-50	and/or	More than 3xULN	50%
	51-85		N/A	25%
	more than 85		N/A	Omit
Rituximab	N/A		N/A	No dose adjustment needed
Vincristine	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	50%
Doxorubicin	less than 10	75%
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

Rituximab

Infusion related adverse reactions have been observed in 12% 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 to if a 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 6 cycles

Drug	Dose	Days	Administration
Cyclophosphamide	400mg/m^2	1	Intravenous bolus over 10 minutes
Doxorubicin	25mg/m^2	1	Intravenous bolus over 10 minutes
Rituximab	375mg/m^2	1	Intravenous infusion in 500ml sodium chloride 0.9%
Vincristine	1mg	1	Intravenous bolus in 50ml sodium chloride 0.9% over 10 minutes
Prednisolone	40mg/m^2	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 (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
- Prednisolone tablets will be rounded to the nearest 5mg (up if half way)
- Rituximab will be dose rounded to the nearest 100mg (up if half way)
- Vincristine dose will be dose banded in accordance with the national dose bands (1mg/ml).

Administration Information

Extravasation

- Cyclophosphamide – neutral
- Doxorubicin – vesicant
- 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.

Additional Therapy

- Antiemetics

15-30 minutes prior to chemotherapy

- ondansetron 8mg oral or intravenous bolus

As take home medication

- metoclopramide 10mg three times a day when required oral
- ondansetron 8mg twice a day for 3 days oral

- Rituximab pre-medication

30 minutes prior to rituximab

- chlorphenamine 10mg intravenous bolus
- paracetamol 1000mg oral

On the morning of treatment

- prednisolone 40mg/m^2 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 bolus 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 7 days oral for the first cycle only

- Anti-infective prophylaxis:

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

- Growth factor according to local formulary choice. For example:

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

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

- 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.

References

1. Pevrade F, Jardin F, Thieblemont C et al. Attenuated immunochemotherapy regimen (R-miniCHOP) in elderly patients older than 80 years with diffuse large B-cell lymphoma: a multicentre, single-arm, phase 2 trial. Lancet Oncology (2011);12: 460 – 468.
2. Peyrade F et al. Rituximab and reduced dose CHOP (R-mini-CHOP) for patients over 80 years with diffuse large B-cell lymphoma (DLBCL) – Groupe d'Etude Des Lymphomes Del l'Adulte (GELA) Study LNH03-7B. Blood (2010): 116 (21): 853.
3. Sandoz Limited (2021). Cyclophosphamide 1000mg powder for solution for injection or infusion summary for product characteristic. Available from https://www.medicines.org.uk/emc. Accessed 04/07/2022.
4. Accord Healthcare Limited (2016). Doxorubicin 2mg/ml concentrate for solution for infusion summary of product characteristics. Available from https://www.medicines.org.uk/emc. Accessed 04/07/2022.

5. Roche products limited (2021). MabThera 100mg Concentrate for Solution for Infusion summary for product characteristics. Available from https://www.medicines.org.uk/emc. Accessed 04/07/2022.
6. Hospira UK Ltd (2022). Vincristine 1mg/ml injection summary for product characteristics. Available from https://www.medicines.org.uk/emc. Accessed 04/07/2022.
7. Accord-UK Ltd (2021). Prednisolone 25mg tablets summary of product characteristics. Available from https://www.medicines.org.uk/emc. Accessed 04/07/2022.

REGIMEN SUMMARY

mini-RCHOP (21)-Cyclophosphamide-Doxorubicin-Prednisolone-Rituximab-Vincristine

Cycle 1

1. Warning – Check patient has taken the prednisolone dose
   Administration instructions:
   Please check the patient has taken prednisolone on the morning of rituximab administration. On occasions where individuals attend for treatment and have forgotten to take the prednisolone please administer prednisolone oral 30 minutes prior to rituximab infusion.

2. Chlorphenamine 10mg intravenous bolus
   Administration instructions:
   Administer 30 minutes prior to rituximab infusion

3. Paracetamol 1000mg oral
   Administration instructions:
   Administer 30 minutes prior to rituximab infusion

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

Administration instructions:
Please check the patient has taken prednisolone on the morning of rituximab administration. On occasions where individuals attend for treatment and have forgotten to take the prednisolone please administer prednisolone orally 30 minutes prior to rituximab infusion. The rate of administration of rituximab varies. Please refer to administration guidelines.

5. Ondansetron 8mg oral or intravenous injection
   Administration Instructions
   May be given as 8mg intravenous injection if the oral route is not appropriate

6. Doxorubicin 25mg/ m^2 intravenous bolus over 10 minutes

7. Vincristine 1mg intravenous bolus in 50ml sodium chloride 0.9% over 10 minutes

8. Cyclophosphamide 400mg/ m^2 intravenous bolus over 10 minutes

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

Take Home Medicines

11. Prednisolone 40mg/ m^2 once a day on the morning of the next treatment

Administration instructions:
Take the prescribed dose on the morning of day 1 of the cycle. This is the supply for your next cycle.
The prednisolone may be dispensed as a single supply in one container or as two containers depending on local preference.

12. Prednisolone 40mg/ m^2 once a day for 4 days oral starting on day 2 of the cycle

Administration instructions:
Take the prescribed dose in the morning for four days starting on day 2 of the cycle.
The prednisolone may be dispensed as a single supply in one container or as two containers depending on local preference.

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

Administration instructions:

Please dispense 28 tablets or nearest equivalent pack size

14. Ondansetron 8mg twice a day for 3 days oral starting on the evening of day one of treatment
    Administration Instructions
    Take 8mg twice a day for three days starting on the evening of day 1 of the cycle

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

16. Growth factor according to local formulary choice.
    Administration Instructions
    Dispense according to local formulary choice. For example:
    - filgrastim or bioequivalent 30 million units once a day for 7 days from day 6 subcutaneous
    - lenograstim or bioequivalent 33.6 million units once a day for 7 days from day 6 subcutaneous
    - pegfilgrastim or bioequivalent 6mg **once only** on day 2 subcutaneous

17. Aciclovir 400mg twice a day oral for 21 days
Administration Instructions
Please supply 21 days or an original pack if appropriate

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

Cycles 2, 3, 4 and 5

1. Warning – Check patient has taken the prednisolone dose
Administration instructions:
Please check the patient has taken prednisolone on the morning of rituximab administration. On occasions where individuals attend for treatment and have forgotten to take the prednisolone please administer prednisolone orally 30 minutes prior to rituximab infusion.

2. Chlorphenamine 10mg intravenous bolus
Administration instructions:
Administer 30 minutes prior to rituximab infusion

3. Paracetamol 1000mg oral
Administration instructions:
Administer 30 minutes prior to rituximab infusion

4. Rituximab 375mg/ m^2 intravenous infusion in 500ml sodium chloride 0.9% as per the rituximab administration guidelines
Administration instructions:
Please check the patient has taken prednisolone on the morning of rituximab administration. On occasions where individuals attend for treatment and have forgotten to take the prednisolone please administer prednisolone orally 30 minutes prior to rituximab infusion. The rate of administration of rituximab varies. Please refer to administration guidelines.

5. Ondansetron 8mg oral or intravenous injection
    Administration Instructions
    May be given as 8mg intravenous injection if the oral route is not appropriate

6. Doxorubicin 25mg/ m^2 intravenous bolus over 10 minutes

7. Vincristine 1mg intravenous bolus in 50ml sodium chloride 0.9% over 10 minutes

8. Cyclophosphamide 400mg/ m^2intravenous bolus over 10 minutes

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

Administration Instructions
when required for the relief of rituximab infusion related reactions

Take Home Medicines

11. Prednisolone 40mg/ m^2 once a day on the morning of the next treatment

Administration instructions:
Take the prescribed dose on the morning of day 1 of the cycle. This is the supply for your next cycle.
The prednisolone may be dispensed as a single supply in one container or as two containers depending on local preference

12. Prednisolone 40mg/ m^2 once a day for 4 days starting on day 2 oral

Administration instructions:
Take the prescribed dose in the morning for four days starting on day 2 of the cycle.
The prednisolone may be dispensed as a single supply in one container or as two containers depending on local preference.

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

Administration instructions:
Please dispense 28 tablets or nearest equivalent pack size

14. Ondansetron 8mg twice a day for 3 days oral starting on the evening of day one of treatment

Administration Instructions
Take 8mg twice a day for three days starting on the evening of day 1 of the cycle

15. Growth factor according to local formulary choice. For example:

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

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

Administration Instructions
Please supply 21 days or an original pack if appropriate

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

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

Cycle 6

1. Warning – Check patient has taken the prednisolone dose

Administration instructions:
Please check the patient has taken prednisolone on the morning of rituximab administration. On occasions where individuals attend for treatment and have forgotten to take the prednisolone please administer prednisolone orally 30 minutes prior to rituximab infusion.

2. Chlorphenamine 10mg intravenous bolus

Administration instructions:
Administer 30 minutes prior to rituximab infusion

3. Paracetamol 1000mg oral

Administration instructions:
Administer 30 minutes prior to rituximab infusion

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

Administration instructions:

Please check the patient has taken prednisolone on the morning of rituximab administration. On occasions where individuals attend for treatment and have forgotten to take the prednisolone please administer prednisolone orally 30 minutes prior to rituximab infusion. The rate of administration of rituximab varies. Please refer to administration guidelines.

5. Ondansetron 8mg oral or intravenous injection
   Administration Instructions
   May be given as 8mg intravenous injection if the oral route is not appropriate

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

7. Vincristine 1mg intravenous bolus in 50ml sodium chloride 0.9% over 10 minutes

8. Cyclophosphamide 400mg/ m^2 intravenous bolus over 10 minutes

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

Take Home Medicines

11. Prednisolone 40mg/ m^2 once a day for 4 days starting on day 2 of the cycle oral
   Administration instructions:
   Take the prescribed dose in the morning for four days starting on day 2 of the cycle
   The prednisolone may be dispensed as a single supply in one container or as two containers depending on local preference.

12. Metoclopramide 10mg three times a day when required oral
Administration instructions:
Please dispense 28 tablets or nearest equivalent pack size

13. Ondansetron 8mg twice a day for 3 days oral starting on the evening of day one of treatment
   Administration Instructions
   Take 8mg twice a day for three days starting on the evening of day 1 of the cycle

14. Growth factor to be continued until the neutrophil count is above $1x10^9$/L. For
   Administration Instructions
   Dispense according to local formulary choice. For example:
   - filgrastim or bioequivalent 30 million units once a day for 7 days from day 6 subcutaneous
   - lenograstim or bioequivalent 33.6 million units once a day for 7 days from day 6 subcutaneous
   - pegfilgrastim or bioequivalent 6mg **once only** on day 2 subcutaneous

15. Aciclovir 400mg twice a day oral for 21 days
Administration Instructions
Please supply 21 days or an original pack if appropriate

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

DOCUMENT CONTROL

Version	Date	Amendment	Written by	Approved by
1	July 2022	n/a	Alexandra Pritchard Pharmacist	Dr Rob Lown Consultant

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 Hospital NHS Foundation Trust
University Hospital Southampton NHS Foundation Trust
Western Sussex 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.